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HOWARD C. TAYLOR, JR. WILLIAM J. DIECKMANN

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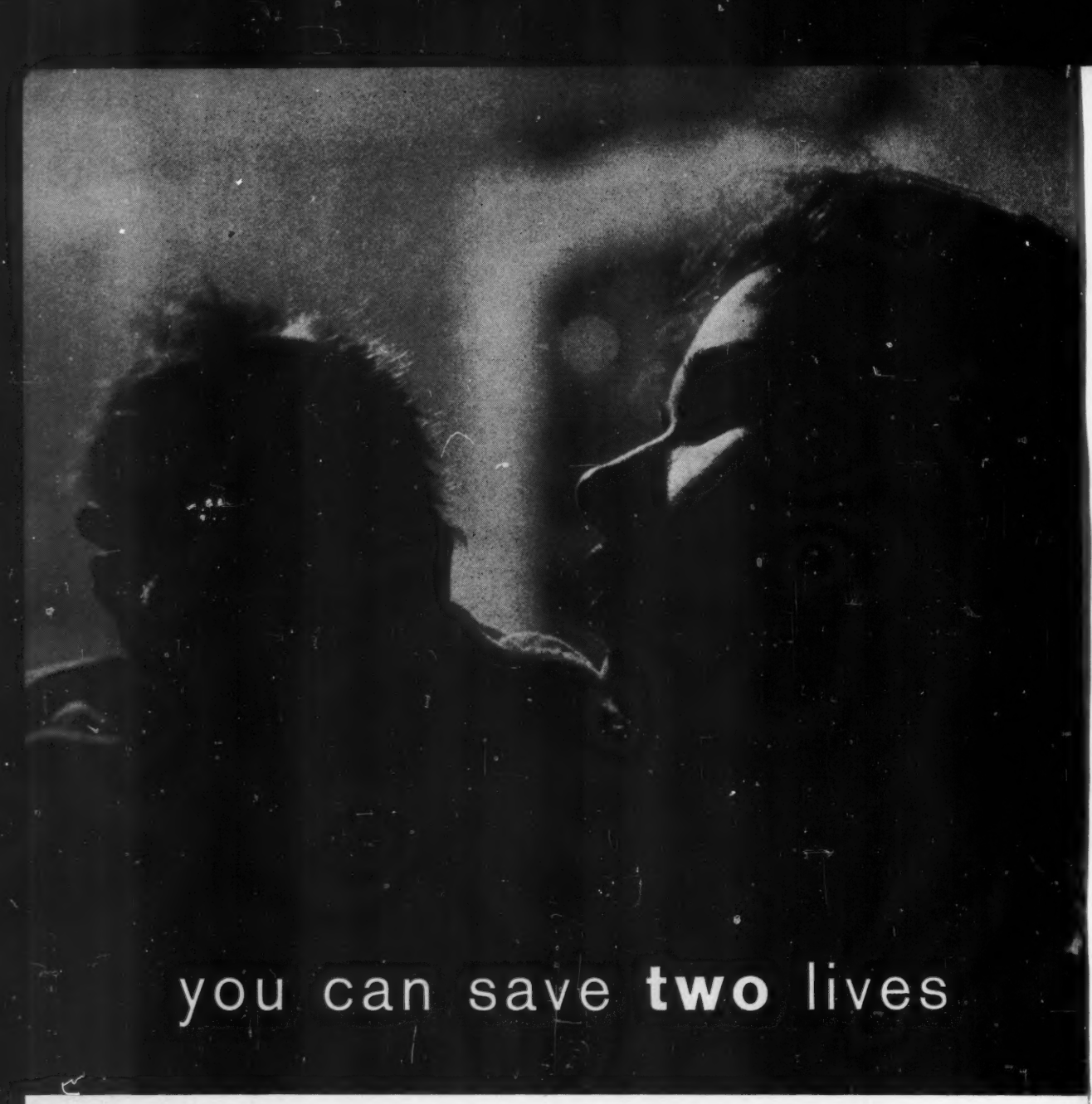

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Reference: 1. Lindley, J. E., Rogers, S. F., and Moyer, J. H.: GP *14*:96 (Aug.) 1956.

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'Thorazine' reduces the need for resuscitation . . .

	'THORAZINE' GROUP		CONTROL GROUP	
anesthetic	Spinal	General	Spinal	General
patients	118	17	105	45
mild resuscitation (oxygen by face mask)	6.8%	17.7%	13.3%	31.0%
active resuscitation (aspiration with tracheal catheter; oxygen via catheter or positive pressure resuscitation apparatus)	none	none	1.9%	6.7%
total	6.8%	17.7%	15.2%	37.7%

The above chart shows the significant decrease—more than half—in the incidence of narcotized and apneic infants obtained by Anz and Smith[1] following their use of 'Thorazine'-potentiated analgesia. (Further information available on request.)

1 Anz, U.E., and Smith, L.J.: Am. J. Obst. & Gynec. 71:1242 (June) 1956.

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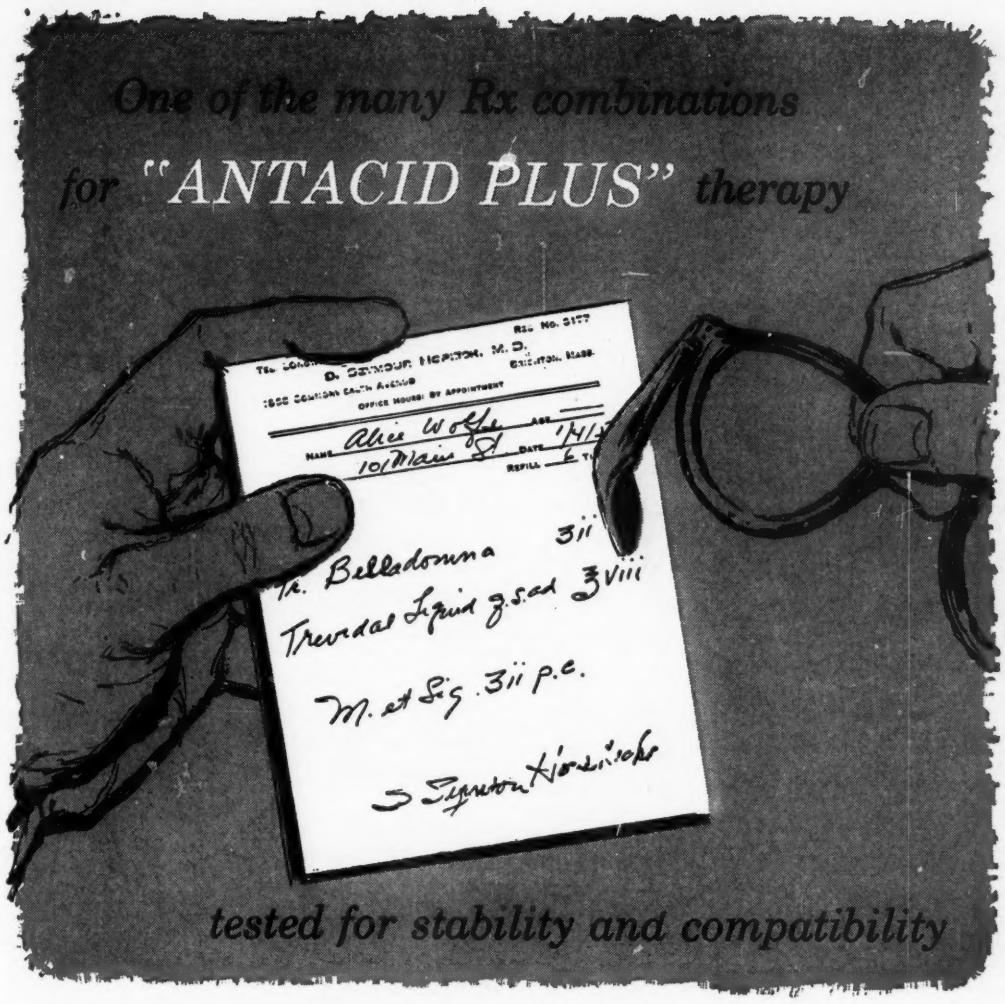
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1. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. *14*:531 (May) 1954. **2.** Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. *15*:206 (Jan.) 1955. **3.** Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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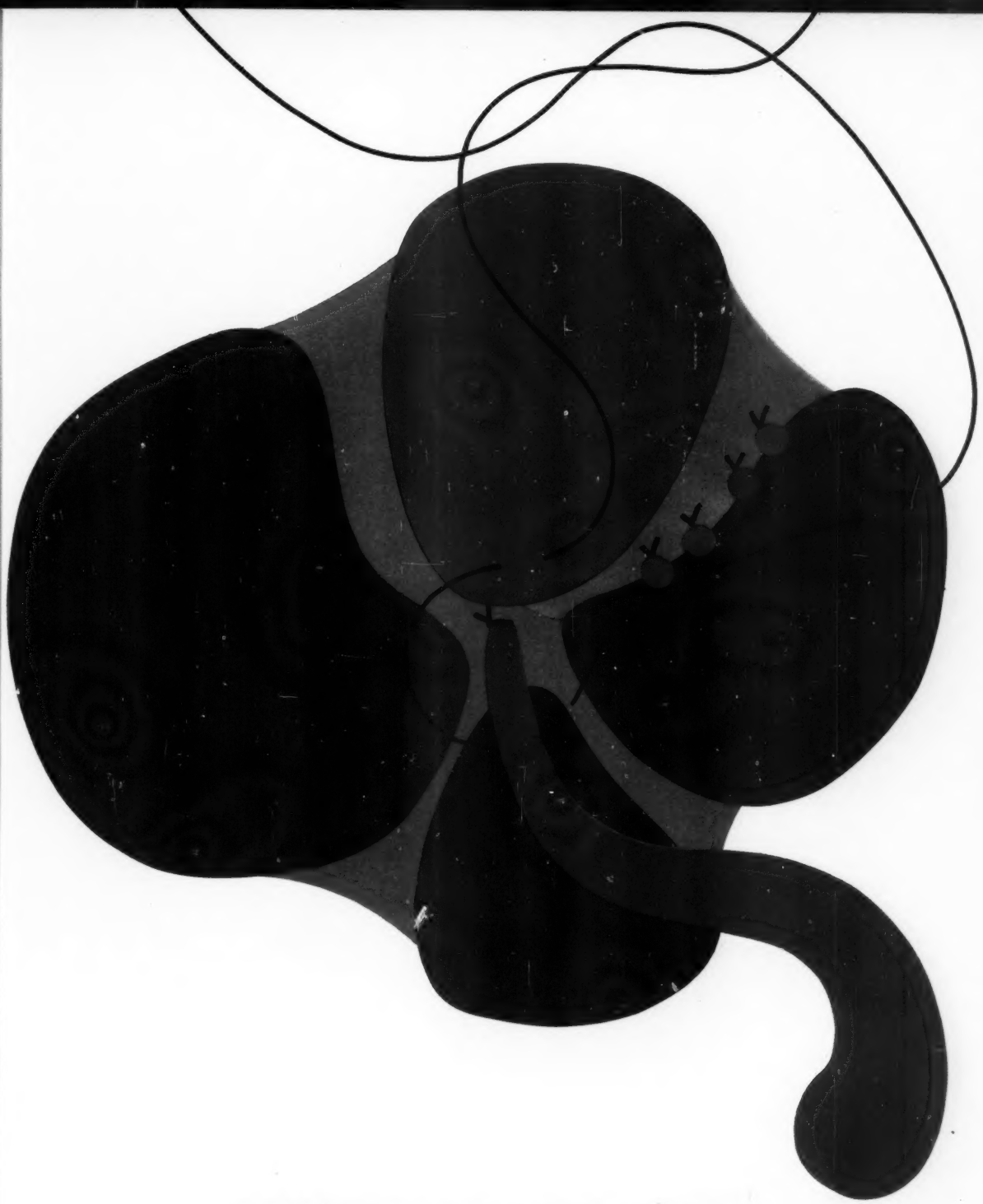

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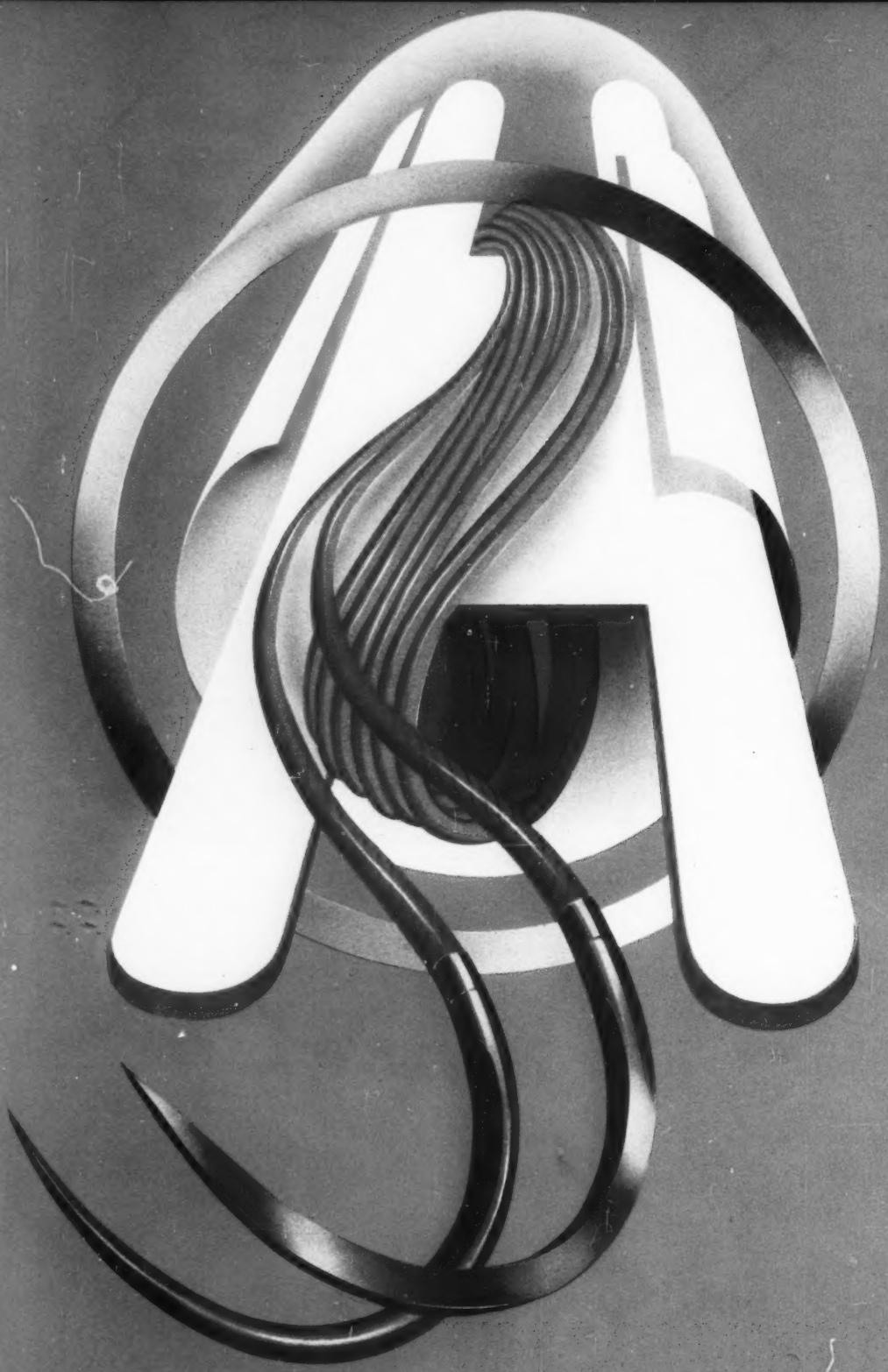

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References: (1) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. I, p. 25. (2) Gaisford, W., and Jennison, R. F.: Brit. M. J. 2:700 (Sept. 17) 1955. (3) Wallerstein, R. O.: J. Pediat. *49*:173, 1956. (4) Sturgeon, P.: Pediatrics *18*:267, 1956. (5) Jennison, R. F., and Ellis, H. R.: Lancet *2*:1245 (Dec. 18) 1954. (6) Scott, J. M., and Govan, A. D. T.: Brit. M. J. 2:1257 (Nov. 27) 1954. (7) Grunberg, A., and Blair, J. L.: A.M.A. Arch. Int. Med. *96*:731, 1955. (8) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. *15*:51, 1956. (9) Baird, I. M., and Podmore, D. A.: Lancet *2*:942 (Nov. 6) 1954. (10) Cappell, D. F.; Hutchinson, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. 2:1255 (Nov. 27) 1954. (11) Stevens, A. R.: A.M.A. Arch. Int. Med. *96*:550 1956.

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Trichotine douches – incorporating the multiple advantages of sodium lauryl sulfate with the recognized values of other specific or adjunctive agents – may be prescribed as often as required in cases of nonspecific vaginitis and leukorrhea, subacute and chronic cervicitis, senile vaginitis, trichomoniasis, and moniliasis; hot packs are often quickly effective in pruritus vulvae.

Concentrated solutions are useful for clean-up or swab treatment in the physician's office.

VACID

the 24-hour vaginal pH stabilizer

The therapeutic value of continual maintenance of normal vaginal pH (4.0 to 4.5) is widely recognized in the treatment of monilial, trichomonal, and nonspecific bacterial infections and in cervicitis.

One Vacid insert suppository will hold the pH of the vagina at the normal physiologic level for 24 hours. Symptomatic relief is noted usually the first day and progressive improvement continues until Doderlein bacilli replace the infecting organisms – usually within 7-14 days.

Samples and literature on request . . . Full details in PDR.

The Fesler Co., Inc. Stamford, Conn.

NOW—the unequalled advantages of K_1—orally

Tablets

MEPHYTON®

(VITAMIN K_1, MERCK)

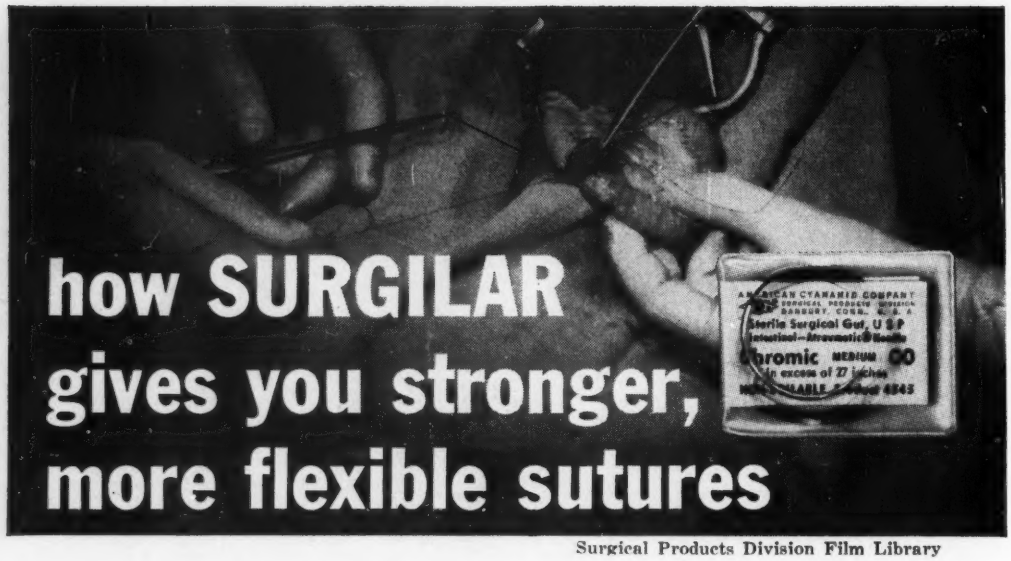
". . . vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] "Vitamin K_1 appears to be equally effective by the oral or intravenous route."[2] Beneficial effects are apparent in 6 to 10 hours following oral use.

Supplied: Oral MEPHYTON—tablets of 5 mg. of vitamin K_1, in bottles of 100. Emulsion of MEPHYTON—in boxes of six 1-cc. ampuls, 50 mg. of K_1 per cc.

References: 1. Gamble, J.R., et al. Arch. Int. Med. 95:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. 42:805, 1953.

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC. PHILADELPHIA 1, PA.



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eliminates glass damage . . . ends excessive handling[1]

No nicked sutures . . . no glass slivers . . . no punctured gloves. SURGILAR has no reel to cause kinks and bends . . . *loose-coil* gut gets much less handling, is noticeably more flexible. Envelope may be easily opened as needed so suture can't dry out. Jar solution is nonirritating.

saves 33⅓% nurse time[1]

Faster handling frees her for other duties . . . new nurses learn simple SURGILAR technic in minutes.

reduces surgical costs[1]

Less accidental breakage . . . fewer sutures opened per operation . . . takes 50% less storage space . . . *costs no more than tubes.*

1. Alexander, Edythe L.: Mod. Hosp., May, 1957.

MORE THAN 1,500 HOSPITALS HAVE ALREADY SWITCHED TO—

D&G SURGILAR®

Sterile Pack
Standard Lengths

Surgical Gut
ATRAUMATIC® Needles

NEW! Spiral Wound Gut
now available in SURGILAR pack!

Write for new catalog of *hospital-tested* products

SURGICAL PRODUCTS DIVISION, AMERICAN CYANAMID COMPANY, DANBURY, CONN

CYANAMID PRODUCERS OF DAVIS & GECK SUTURES

specifically for reduction of overweight

PRELUDIN®

(brand of phenmetrazine hydrochloride)

"...a highly effective and safe appetite suppressant..."[1]

Based on clinical reports, PRELUDIN produces more than twice the weight loss achieved by patients receiving a placebo.[2] It is singularly free of tendency to produce serious side actions, as well as stimulation.[1-3] PRELUDIN imparts a feeling of well-being that encourages the patient to cooperate willingly in treatment.[1-3]

The reduced incidence of side actions with PRELUDIN makes losing weight more comfortable for the average patient, facilitates treatment of the complicated case and frequently permits its use where other anorexiants are not tolerated.[3]

Recommended Dosage: One tablet two to three times daily one hour before meals. Occasionally smaller dosage suffices. On theoretical grounds, PRELUDIN should not be given to patients with severe hypertension, thyrotoxicosis or acute coronary disease.

(1) Holt, J. O. S., Jr.: Dallas Med. J. 42:497, 1956. (2) Gelvin, E. P.; McGavack, T. H., and Kenigsberg, S.: Am. J. Digest. Dis. 1:155, 1956. (3) Natenshon, A. L.: Am. Pract. & Digest Treat. 7:1456, 1956.

PRELUDIN® (brand of phenmetrazine hydrochloride). Scored, square, pink tablets of 25 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

GEIGY Ardsley, New York 77857

"Really?"

Yes...

desPLEX®

to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

recommended for routine prophylaxis in ALL pregnancies . . .

96 per cent live delivery with desPLEX in one series of 1200 patients[4]— — bigger and stronger babies, too.[cf. 1]

No gastric or other side effects with desPLEX — in either high or low dosage[3,4,5]

(Each **des**PLEX tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating *to assure prompt help in emergencies.* **des**PLEX tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

For further data and a generous trial supply of **des**PLEX, write to:
Medical Director

REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
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4. Peña, E. F.: Med. Times 82:921, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

me	Address	Tel No.	Occupation	Age
Edwards, Iva (Mrs.)	672 5th Ave.	AB 4-4134	Laundry	43

JCM 484331

Ref. by Mrs. Wilson

ate:

2/4/57 Heavy set, works in hot environment, nylon bra. Eruption under breasts - folliculitis, 1 day - erythema, 3 days - eczematized eruption past week - pruritus, weeping, fissure. Has used several 'salves' and drying lotions, caused burning and spread.

FH-PH: No diabetes, systemic disease

Dx: Intertrigo, inframammary

Worth trying—

PRODUCT INFORMATION

TASHAN CREAM 'Roche'

SOOTHING, HEALING MULTIVITAMIN SKIN CREAM

DESCRIPTION: Tashan Cream provides four vitamins to help maintain skin health and promote healing.

Each gram (approx. 1/30 ounce) contains:

Vitamin A	10,000 U.S.P. units
Vitamin D_2	1,000 U.S.P. units
d-Panthenol	50 mg (5%)
Vitamin E (*dl*-alpha-tocopheryl acetate)	5 mg

in a cosmetically pleasing, vanishing cream type base.

PROPERTIES: Vitamins A and D help maintain skin health; inhibit keratin formation; promote smoother, softer skin. Vitamin E is antipruritic; exerts a trophic effect through stimulation of skin metabolism. Panthenol is essential for integrity of tissue in general, promotes epithelization.

INDICATIONS: To relieve symptoms and promote healing in skin disorders characterized by itching, dryness, fissures, superficial ulceration, delayed cicatrization, etc., including:

Eczema	Nipple conditioning
Diaper rash	Minor burns
Prickly heat	Contact dermatitis
Intertrigo, chapping	Pruritus ani and vulvae
Sunburn, windburn	Diabetic skin disorders
Decubitus ulcers	Excoriation

DOSAGE: Apply a thin layer of Tashan Cream and rub in gently, three or more times daily.

PACKAGES: 1 ounce tubes.

Tashan®

Hoffmann-La Roche Inc • Nutley • New Jersey

Bactericidal! Fungicidal!

DERMOPLAST® aerosol

TOPICAL ANESTHETIC • ANTIPRURITIC • ASTRINGENT

IN OBS & GYN USE

NEW—3 OZ.
PRESCRIPTION SIZE

for individual therapy in hospital and home.

Also available in . . .

HOSPITAL economy size .... 12 oz.
JUNIOR size ..... 6 oz.

PROVIDES NEW RELIEF OF SURFACE PAIN AND ITCHING ON CONTACT WITHOUT TOUCHING AFFECTED AREAS

perineal suturing
hemorrhoids
pruritus ani
pruritus vulvae
wounds
burns
abrasions
sunburn

FORMULA: benzocaine 4.7%; benzethonium chloride 0.1%; menthol 0.5%; dissolved in oils (Doho process)

Substantiating clinical data sent on request

MALLON DIVISION
DOHO
100 VARICK ST.
NEW YORK 13, N. Y.

Local Estrogen Application Greatly Simplifies Treatment of Senile Vaginitis.

This method provides an "almost immediate healing and soothing effect" Doyle reports,[1] and "is a valuable therapeutic constituent in the management of vaginitis and vaginal infections, regardless of etiology."[2] This worker employed "Premarin" Vaginal Cream applied locally and found it "superior" to the use of suppositories. In addition, there was none of the "side-effects frequently noted with synthetic products . . ."[1]

Favors Rapid Healing in Vaginal Surgery

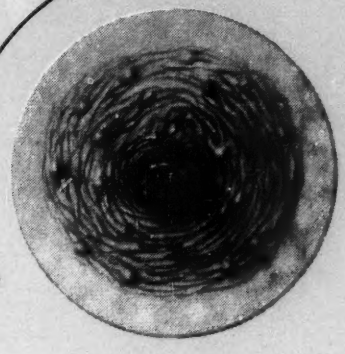
In plastic vaginal surgery in the postmenopausal patient, local estrogen application prior to and after intervention will restore the atrophic and friable mucosa to a more youthful state by promoting proliferation and vascularity of the epithelium. This will facilitate the surgical procedure as well as favor more rapid healing.[2,3]

"PREMARIN®" VAGINAL CREAM in a nonliquefying base, is standardized in terms of the weight of active, water-soluble estrogen content expressed as sodium estrone sulfate (0.625 mg. per gram). Presented in a combination package No. 874 — 1½ oz. tube with specially designed calibrated applicator; also refill available. Complete information may be obtained by writing to Ayerst Laboratories, 22 East 40th Street, New York 16, N. Y.

1. Doyle, J. C.: California Med. *71*:15 (July) 1949. • 2. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 3. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657.

5557

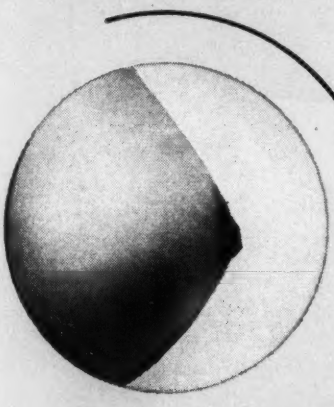
Ayerst Laboratories • New York, N. Y. • Montreal, Canada



FISSURED NIPPLE THERAPY

The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.

WHITE'S VITAMIN A & D OINTMENT

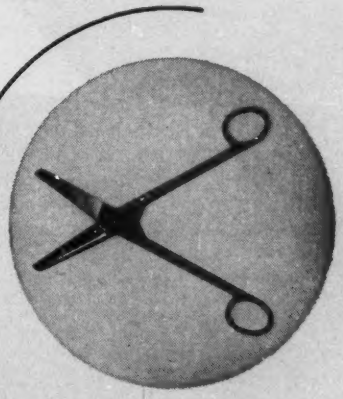


NIPPLE ROUTINE

—a valuable and simple prophylactic measure against drying, fissuring and erosion.

AFTER EPISIOTOMIES

As a post-surgical dressing, White's Vitamin A & D Ointment provides comfort for the patient and encourages rapid healing.



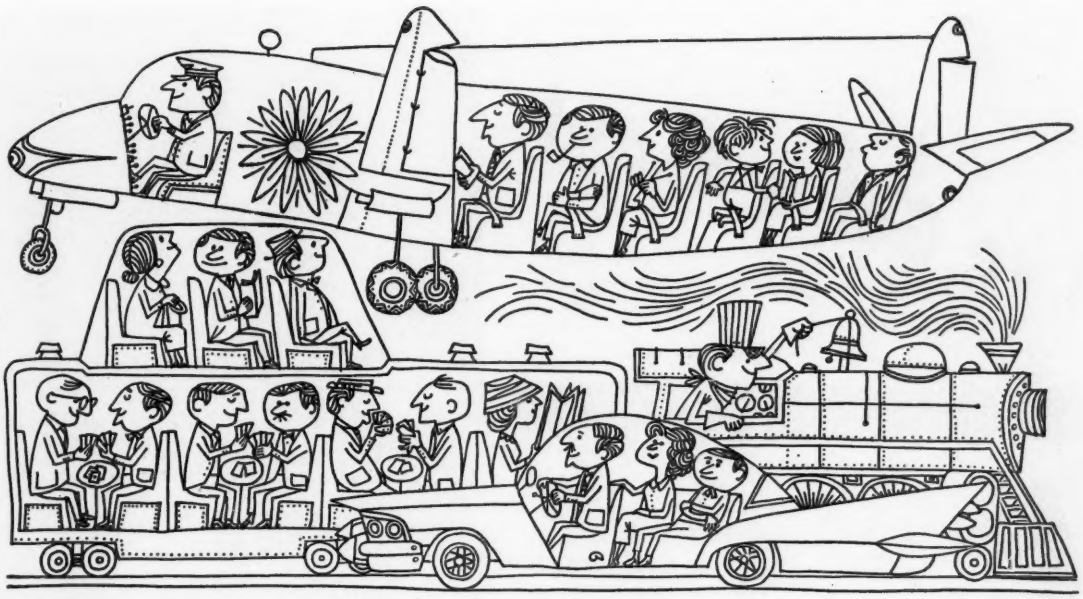
Specify White's Vitamin A & D Ointment also in such conditions as burns, diaper rash, chafing, indolent ulcers.
Recommend the 1½ or 4 oz. tubes; the 1 lb. or 5 lb. jars.

White's

WHITE LABORATORIES, INC./KENILWORTH, NEW JERSEY

a new
direction
in
surface
anesthesia

Not a "caine" derivative. Good relief was provided in more than 15,600 case studies. Sensitization was negligible, and neither toxicity nor cross-sensitization was observed. Abbott



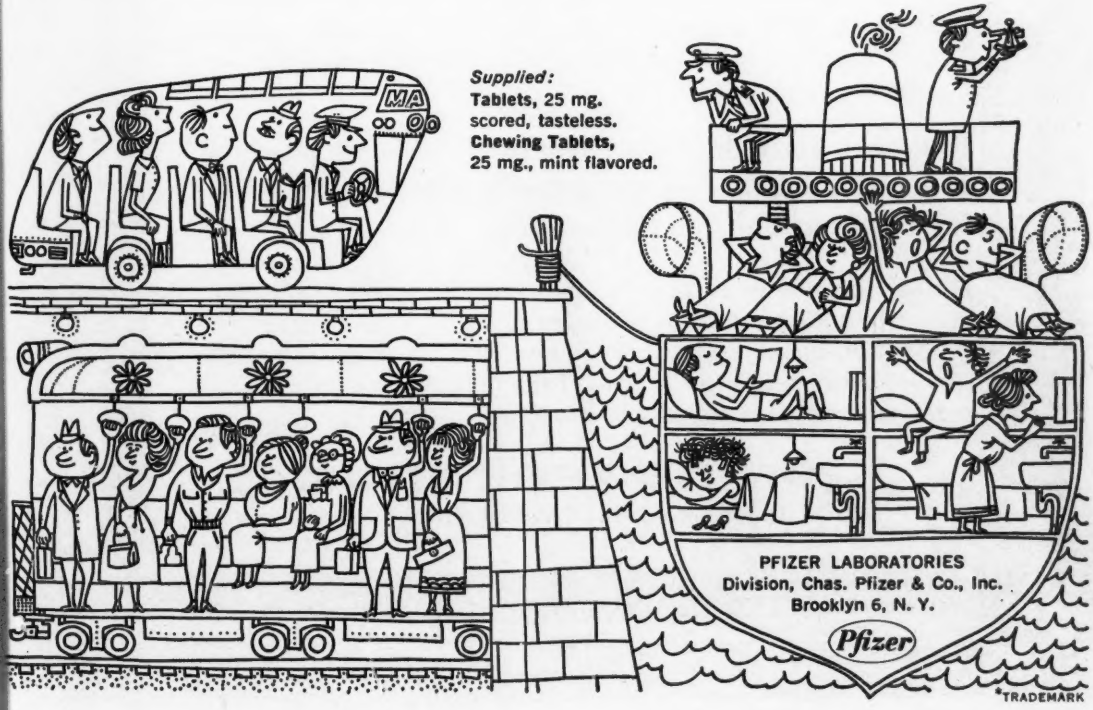
from the depths to the heights

longest acting protection against motion sickness with

Bonamine*

BRAND OF MECLIZINE HYDROCHLORIDE

just one dose prevents motion sickness for 24 hours



Supplied:
Tablets, 25 mg.
scored, tasteless.
Chewing Tablets,
25 mg., mint flavored.

*TRADEMARK

I've Got a Secret

It's probably that he has a frog in his pocket... but his mother also has a secret... she's going to have a baby.

This intelligent modern mother has placed herself in the care of the physician in whom she has implicit faith. Now, the Doctor may, and probably does, prescribe a number of different prenatal supplements to his patients for various but valid reasons.

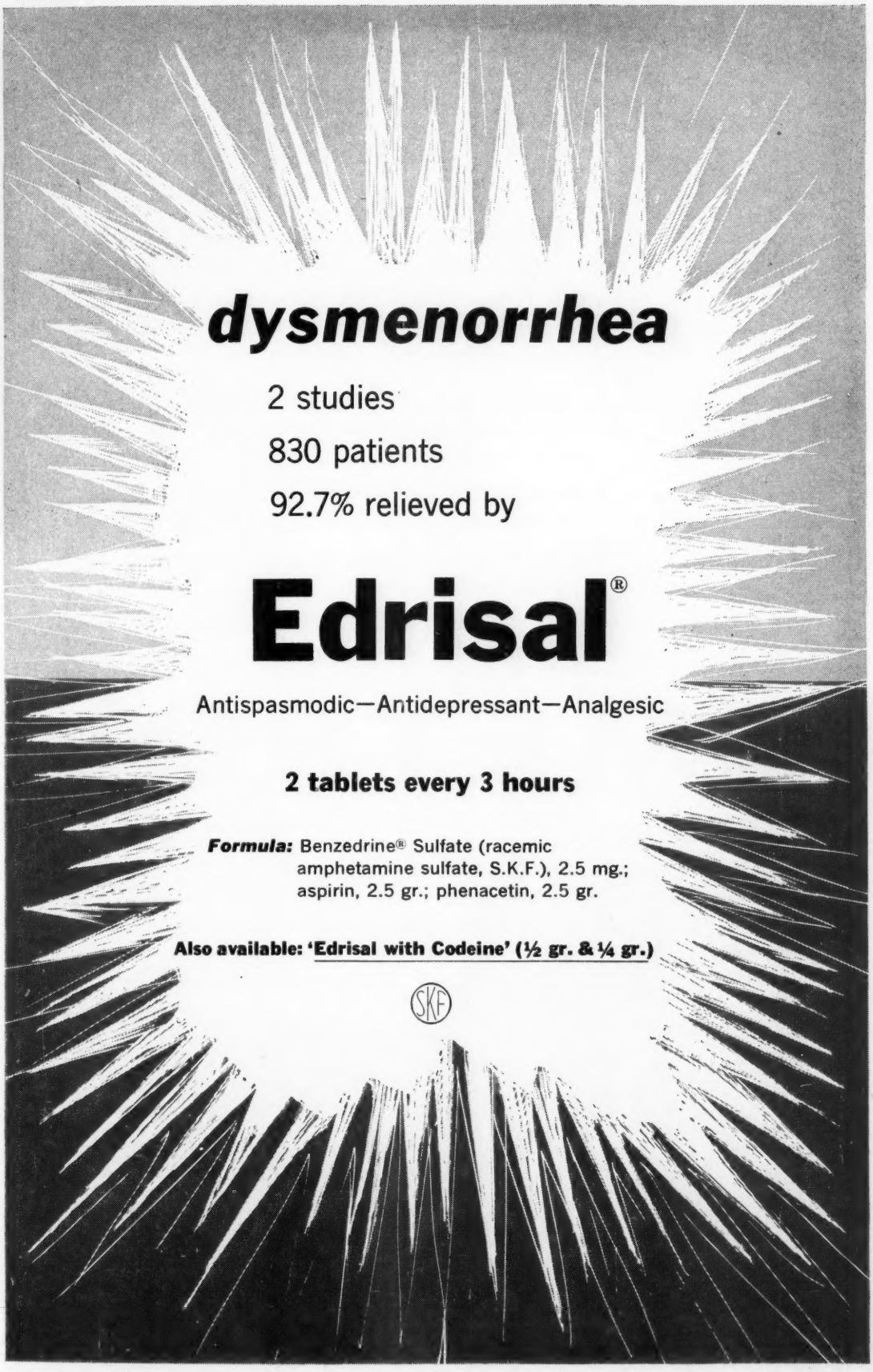
It is quite possible, indeed probable, that the physician may consider the use of a phosphorus-free, aluminum hydroxide containing product. Especially if it also provides organic iron, Vitamin B12 with intrinsic factor, plus the *important* vitamins in the *new* levels suggested for pregnant or lactating women. There are only a very *few* such quality formulas available for his choice.

One such formula with perhaps the easiest product name to remember on the national scene is Calcinatal® *(pronounced Calci' natal)* by Nion.

Patient acceptance of these easy-to-swallow tablets (not capsules) is quite understandable. Incidentally, one of your obstetrical problems, "control of Cramps" will be relegated to one of very minor incidence by use of the product. For more complete information, samples and brochure write to

NION CORPORATION
LOS ANGELES 38, CALIFORNIA

P.S. *We feel copy writers usually mention product names too often . . . . we mention ours but on[ce]. It is so easy to remember and hard to forget. Say it once – try to forget it.*


dysmenorrhea
2 studies
830 patients
92.7% relieved by
Edrisal®
Antispasmodic—Antidepressant—Analgesic
2 tablets every 3 hours
Formula: Benzedrine® Sulfate (racemic amphetamine sulfate, S.K.F.), 2.5 mg.; aspirin, 2.5 gr.; phenacetin, 2.5 gr.
Also available: 'Edrisal with Codeine' (½ gr. & ¼ gr.)
SKF

Safety First | in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.[1-3]
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

EMETROL®

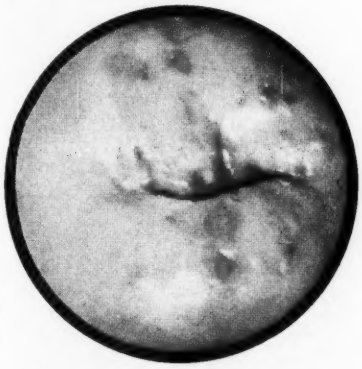
(Phosphorated Carbohydrate Solution)

1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

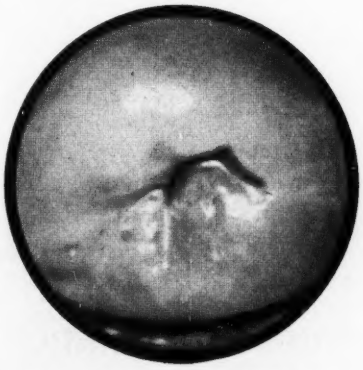
Kinney

KINNEY & COMPANY, INC.
COLUMBUS, INDIANA

Pre-cauterization



2 weeks post-cauterization



3 weeks post-cauterization,
healing nearly complete

PHOTOGRAPHS BY SCHWARTZ, J.: AM. J. OBST. 63:579, 1952.

FASTER HEALING, GREATER PATIENT COMFORT

Whether cauterization, conization, other surgical operation or radiation of the cervix uteri is indicated, FURACIN Vaginal Suppositories can aid materially. Administered before and after these procedures, they eliminate infection; minimize discharge, malodor and irritation; facilitate healing and provide a more rapid and comfortable convalescence. In conjunction with radiotherapy, they control infection and thus contribute to "a better response of the malignant tissue to a given unit of radiation."* FURACIN Vaginal Suppositories do not cause monilial superinfection and are safe for prolonged use.

FORMULA: 0.2% FURACIN in water-miscible base; hermetically sealed in yellow foil.

*Schwartz, J., and Nardiello, V.: Am. J. Obst. 65:1069, 1953.

FURACIN® VAGINAL

BRAND OF NITROFURAZONE SUPPOSITORIES

ALSO AVAILABLE: FURACIN URETHRAL SUPPOSITORIES

NITROFURANS
a new class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES NORWICH, NEW YORK

eliminate pain . . . while maintaining muscle relaxation and patient cooperation . . . **in obstetrical delivery**

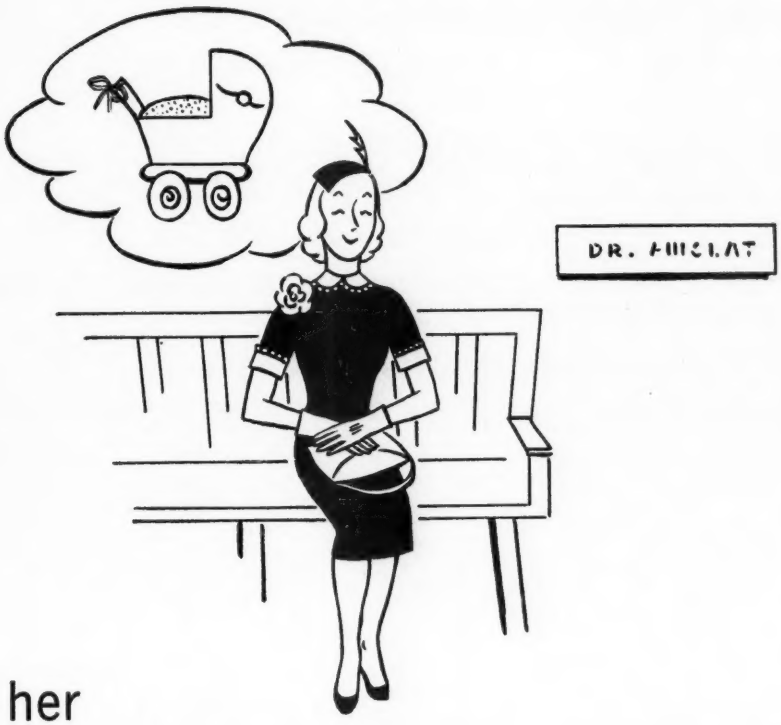
Saddle block with Heavy Solution Nupercaine, testified safe by hundreds of thousands of successful deliveries, fulfills the criteria for ideal obstetrical anesthesia: "*1. An anesthetic that is safe for both mother and baby. 2. An anesthetic that is easy to administer, and one in which personnel can be quickly and easily trained. 3. An anesthetic which alleviates pain of delivery for the patient while still inducing complete relaxation for the benefit of the obstetrician.*"[1]

1. Seegar, J.K.B.E., and Devlin, A.J.: Maryland M.J. 5:330 (June) 1956.

Supplied: 1:400 Nupercaine hydrochloride in 5% dextrose, 2-ml. ampuls, each ml. containing 2.5 mg. Nupercaine and 50 mg. dextrose; cartons of 10.

HEAVY SOLUTION **Nupercaine®**
hydrochloride
(dibucaine hydrochloride with dextrose 5% CIBA)

CI
SUMMIT,



assure her

a more serene, a happier pregnancy
. . . without nausea

give her **'MAREDOX'®** brand

Cyclizine Hydrochloride and Pyridoxine Hydrochloride

because 'Maredox' gives the expectant mother new-found relief from morning sickness.

relieves nausea and vomiting and ***counteracts pyridoxine deficiency*** *in pregnancy*

One tablet a day, taken either on rising or at night, is all that most women require.

Each tablet of 'Maredox' contains:
'Marezine'® brand Cyclizine Hydrochloride. . . . . 50 mg.
Pyridoxine Hydrochloride . . . . . 50 mg.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

Activated Assimilation of Iron

"Our results . . . have been so striking . . . dramatic . . . rapid."[1]

". . . a more rapid and constant hemoglobin rise

. . . with no evidence of toxicity."[2]

Mol-Iron®

Now

Mol-Iron with Vitamin C

*Better tolerated Mol-Iron is now available with vitamin C (75 mg. per tablet), because ascorbic acid has been shown to promote increased absorption of orally administered iron.[15]

Dosage: Adults—2 tablets t.i.d. after meals.
Children—6 to 12 years—1 tablet t.i.d. after meals.

Supplied: Bottles of 100 only.

Well-tolerated—even by patients with a history of iron intolerance.[3, 4]

More rapid maximal hemoglobin response shortens the period of treatment usually necessary with other preparations.

Outstanding efficacy and tolerance is attested by more original investigations and clinical evaluations[1-14] than have been reported for any other iron preparation.

Tablets

ALSO AVAILABLE AS **LIQUID** AND **DROPS**

REFERENCES:

1. Dieckmann, W.J., and Priddle, H.D.: Am. J. Obst. & Gynec. 57:541, 1949.
2. Mercer, J.P., and Zann, G.J.: Report on unpublished data.
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13. Dieckmann, W.J., et al.: Am. J. Obst. & Gynec. 59:442, 1950.
14. Talso, P.J.: J. Insurance Med. 4:31, 1948-49.
15. Coleman D.H., Stevens, H.R., Jr., and Finch, A.C.: Blood, 10:567. 1955.

Dosage: Adults—2 tablets t.i.d. after meals.
Children—6 to 12 years—1 tablet t.i.d. after meals.

Supplied: Tablets in bottles of 100. Liquid in bottles of 12 fluid oz. Drops in bottles of 15 and 50 cc. with calibrated dropper.

WHITE LABORATORIES, INC. • KENILWORTH, N. J.

SAVES TEACHING TIME...

Koro-Flex
TRADE MARK

improved

THE DIAPHRAGM WITH THE

CONTOURING SPRING (ARCING TYPE)

SIX REASONS WHY PHYSICIANS ARE RECOMMENDING Koro-Flex
TRADE MARK

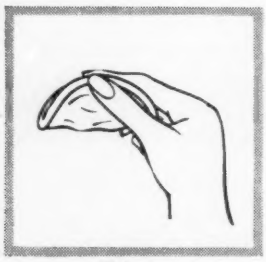


FIG. 1

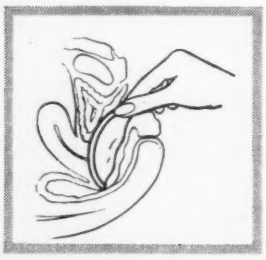


FIG. 2

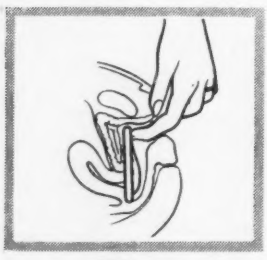


FIG. 3

1. Expressly designed to assure your patient ease of insertion and automatic placement.
2. Conserves physician's time by reducing fitting and instruction period.
3. Patients learn readily and develop greater confidence because of the ease with which they learn to place and use the diaphragm.
4. Affords patient protection by locking in spermicidal lubricant and delivering it directly under and next to the os uteri.
5. Folds behind pubic bone with suction-like action forming an effective barrier.
6. Simple to remove.

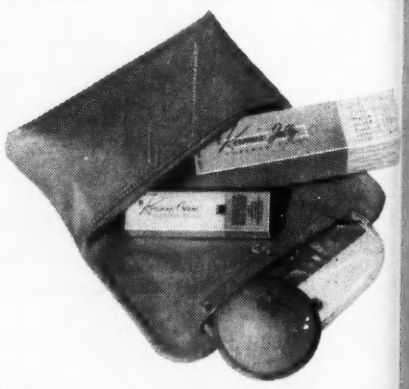
When compressed, diaphragm forms into semi-curve or half-moon shape (Fig. 1) permitting it to pass easily along floor of the vagina beyond cervix (Fig. 2) without any difficulty. No mechanical inserter or introducer required (see Fig. 2) since the KORO-FLEX will not buckle or butterfly in form.

KORO-FLEX (contouring) Diaphragm acceptable, not only where ordinary coilspring diaphragms are indicated but for Flat rim (Mensinga type as well.

May be used in cases of mild prolapse, cystocele or rectocele.

Suggest the convenient-economical KORO-FLEX COMPACT 60-95 mm Sanitary plastic bag with zipper closure. Diaphragm, tube KOROMEX Jelly (3 oz.) Cream (1 oz. trial size).

Available in all prescription pharmacies. Write for descriptive literature.



Holland-Rantos Co., Inc. Manufacturers of **KOROMEX** Products, New York 13, N.

in urinary tract infections of pregnancy delay is dangerous...

"Approximately one-half of the patients have some permanent damage to the urinary tract."[1]

30 min. antibacterial concentrations in urine
24 hrs. turbid urine frequently clear
3 days most patients symptom-free

FURADANTIN® *first...*

BRAND OF NITROFURANTOIN

FOR RAPID ERADICATION OF INFECTION

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REFERENCES: 1. Rives, H. F.: Texas J. M. **52**:224, 1956. 2. Diggs, E. S.; Prevost, E. C., and Valderas, J. G.: Am. J. Obst. **71**:399, 1956. 3. MacLeod, P. F., et al.: Internat. Rec. Med. **169**:561, 1956.

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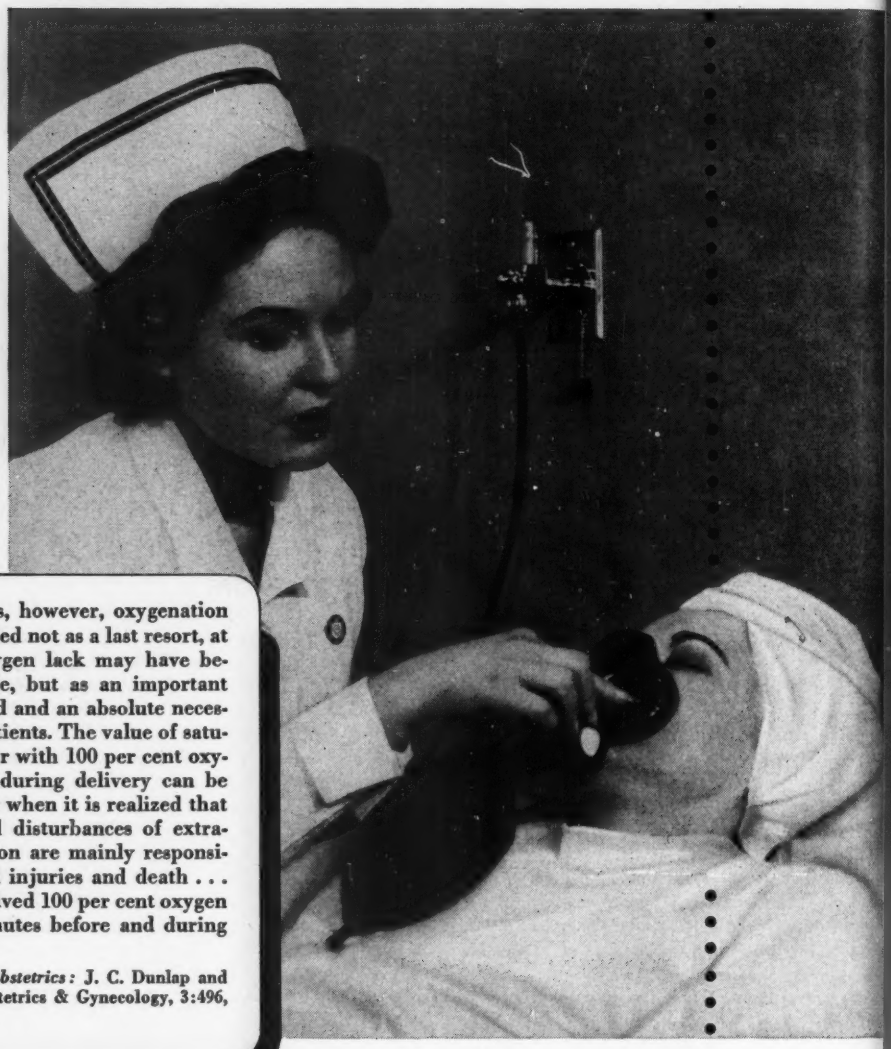

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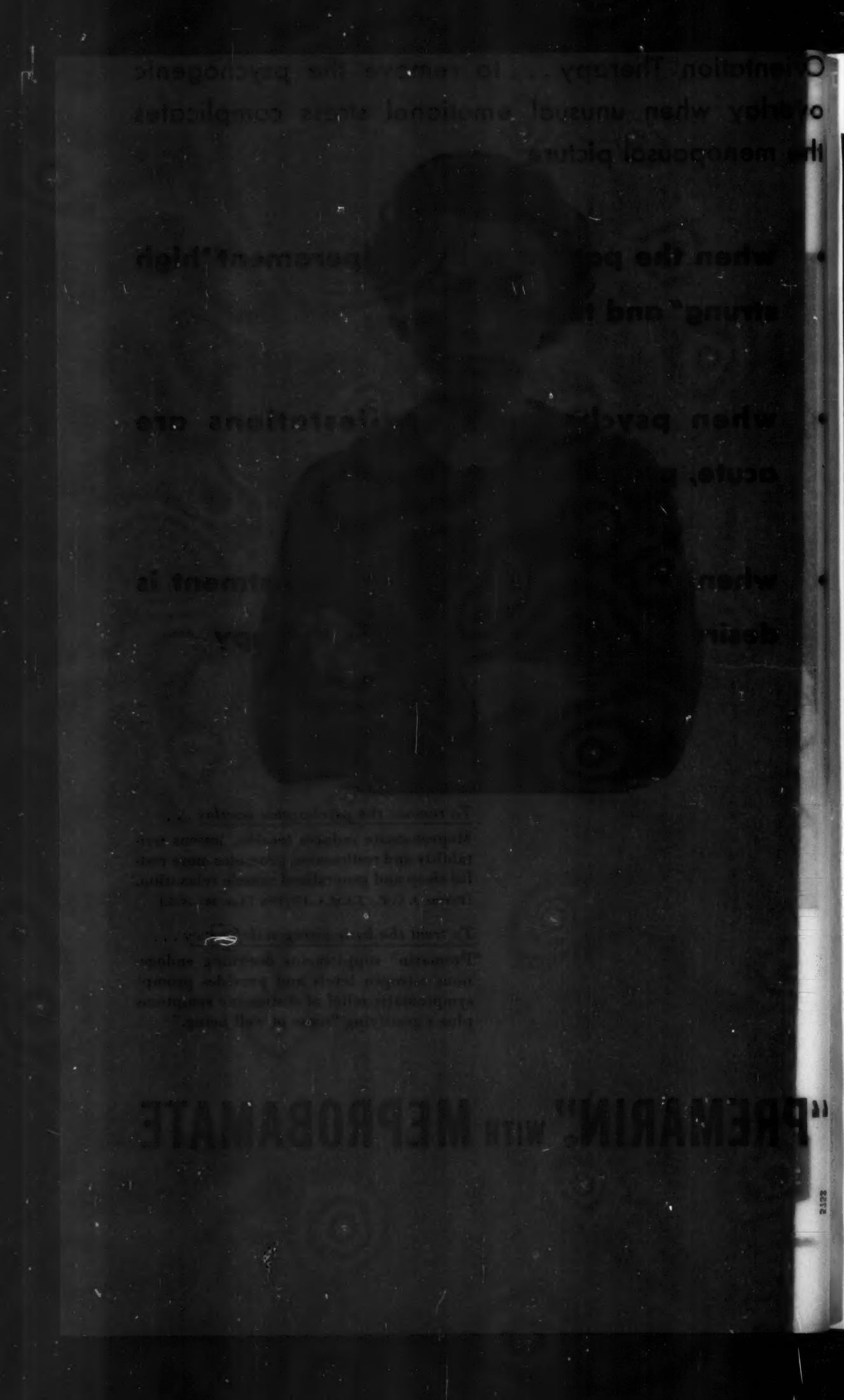

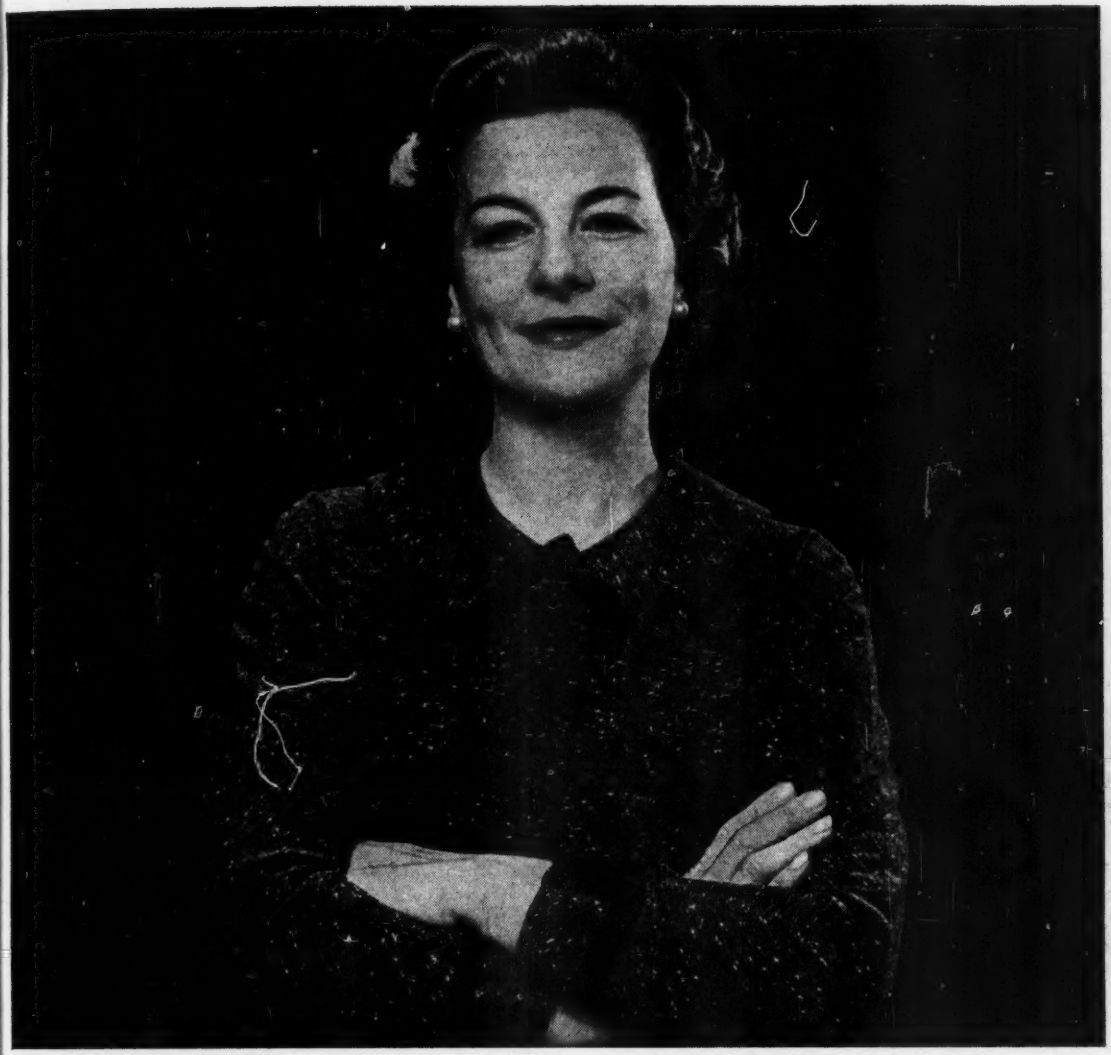

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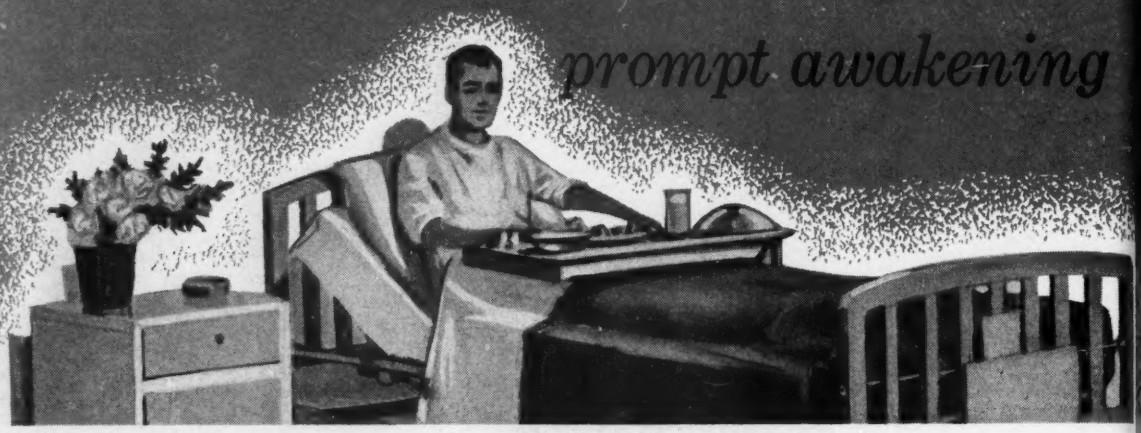

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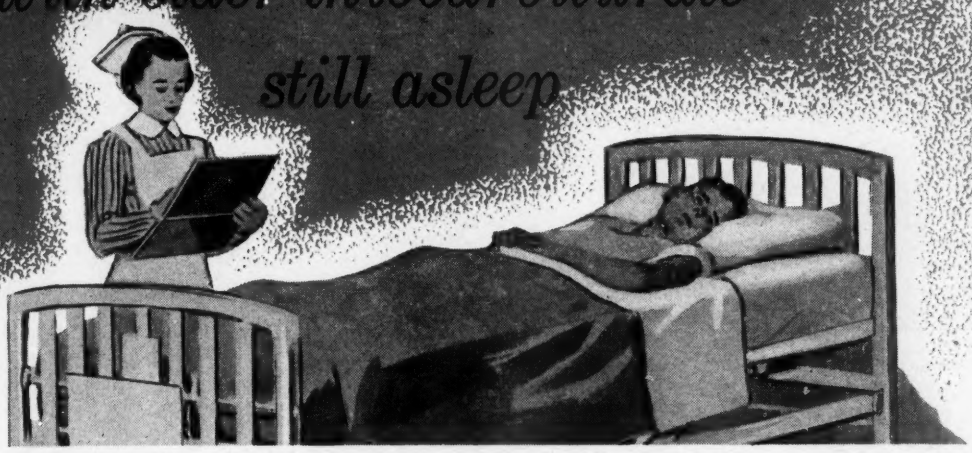

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Bibliography:
(1) Boone, J. D.; Muñoz, R., and Dillon, J. B.: Anesthesiology *17*:284, 1956. (2) Zima, O.; von Werder, F., and Hotovy, R.: Anaesthesist *3*:244, 1954. (3) Mersch, M. A.; Clarie, D'A., and Fitzpatrick, L. J.: J.M. Soc. New Jersey *53*:414, 1956. (4) Blake, M. W., and Perlman, P. L.: J. Pharmacol. & Exper. Therap. *117*:287, 1956. (5) Irwin, S.; Stagg, R. D., Dunbar, E., and Govier, W. M.: J. Pharmacol. & Exper. Therap. *116*:317, 1956. (6) Ayd, F. J., Jr.: Neraval: A new anesthetic for electroconvulsive therapy, Paper presented at annual meet., Electroshock Research Association, Chicago, Illinois, April 29, 1956. (7) Reifferscheid, M., and Dietmann, K.: Deutsche med. Wchnschr. *79*:638, 1954. (8) Houde, J., Hudon, F., and Jacques, A.: Neraval (methitural sodium), Paper presented at Meet., Canad. Anaesth. Soc., Quebec City, P. Q., May 5, 1956.

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References: 1. Greenblatt, R. B.: Obst. & Gynec. *2*:530, 1953. 2. Dill, L. V.: M. Ann. District of Columbia *23*:667, 1954. 3. Greenblatt, R. B.: Ann. New York Acad. Sc. *61*:713, 1955. 4. Javert, C. T.: Obst. & Gynec. *3*:420, 1954. 5. Javert, C. T.: Ann. New York Acad. Sc. *61*:700, 1955. 6. Barishaw, S. B.: Exp. Med. & Surg. *7*:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: Am. J. Digest. Dis. *17*:92, 1950.

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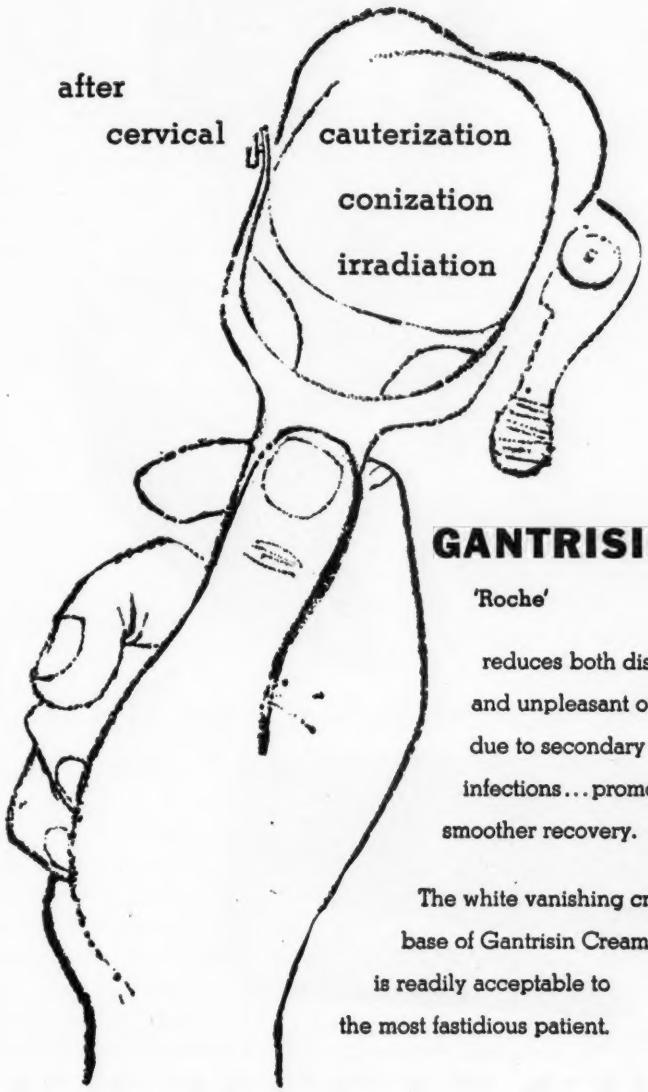

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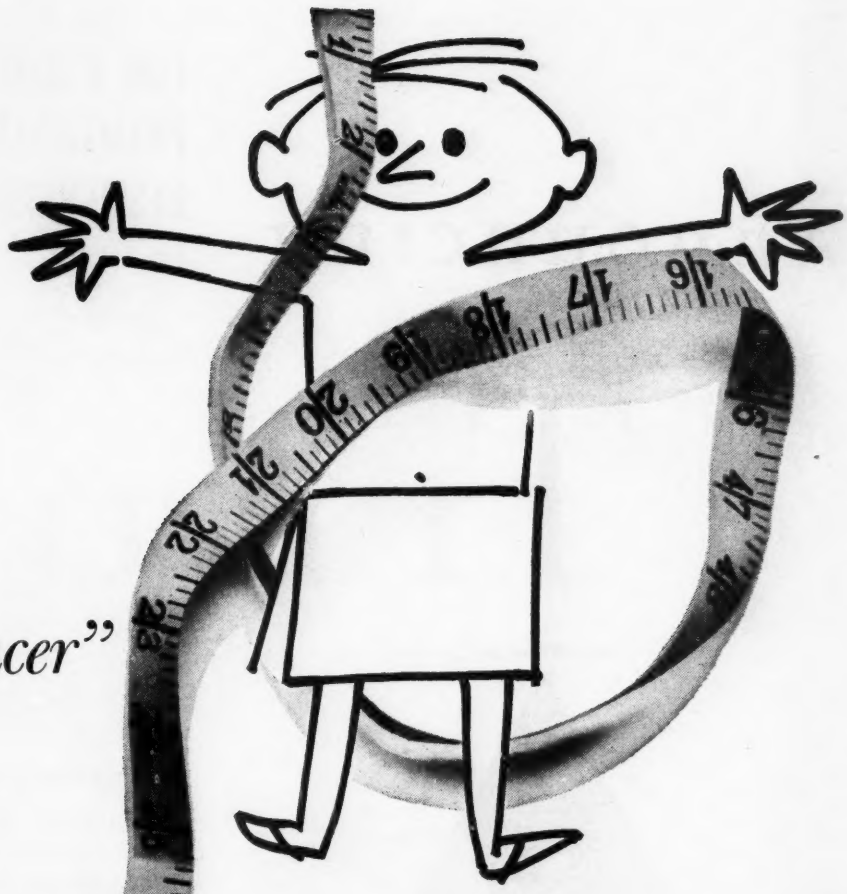

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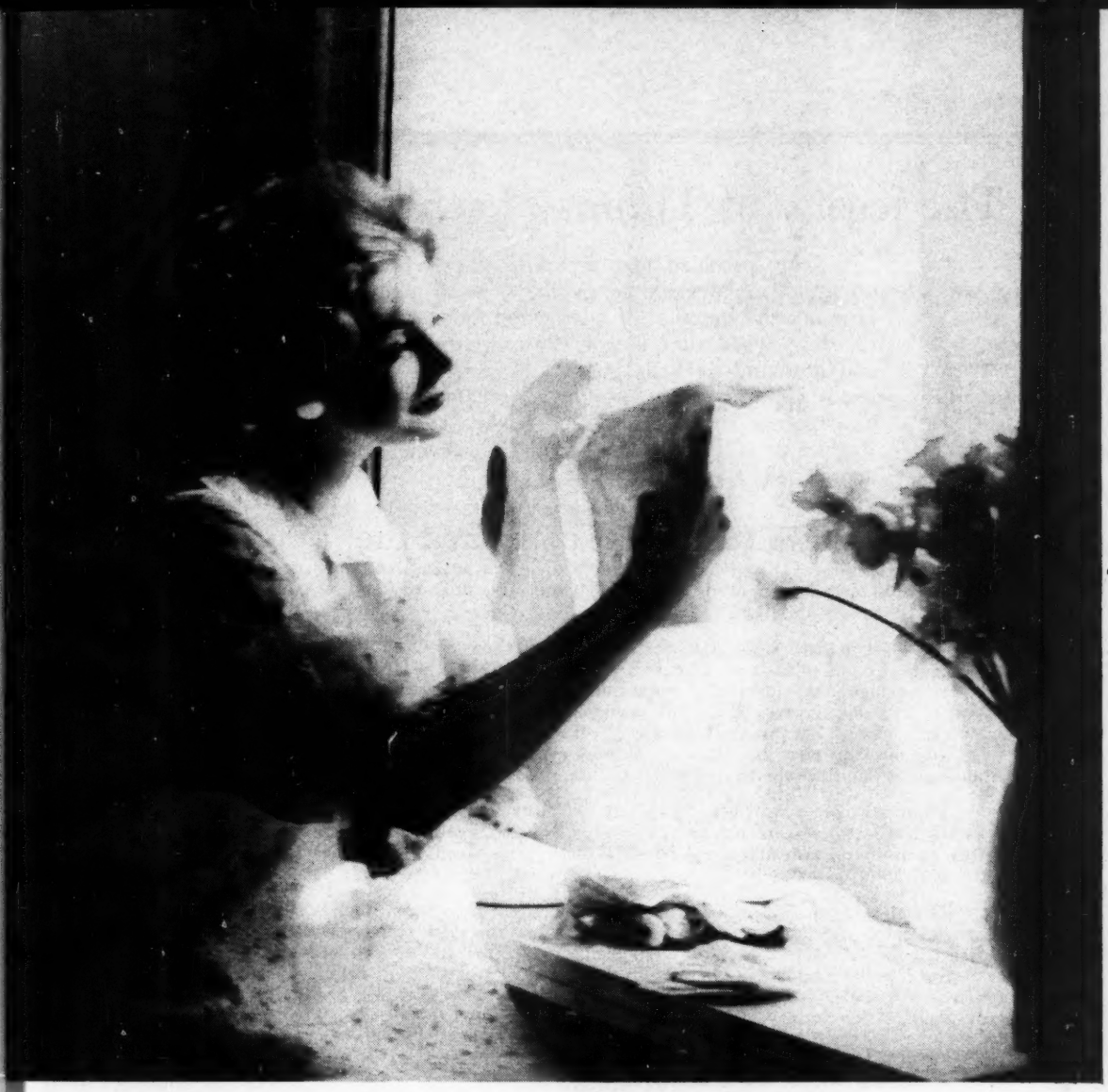

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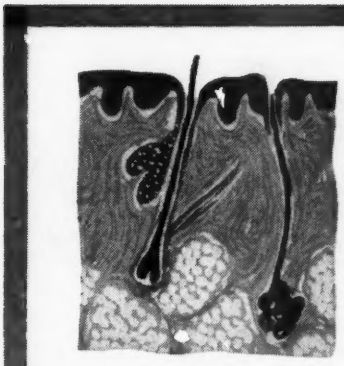

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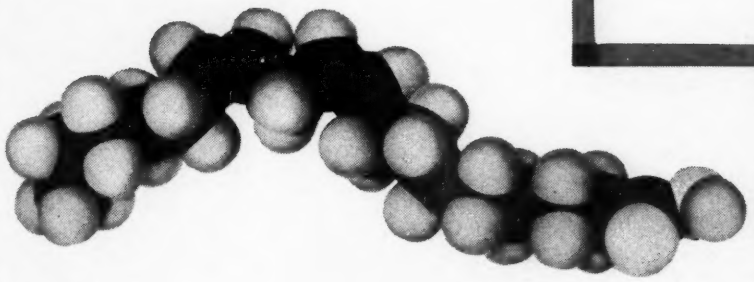

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1. Hansen, A. E.; Adam, D. J. D.; Boelsche, A. N.; Haggard, M. E.; Wiese, H. F.; Pratt, E. L., and Hunter, V.: Fed. Proc. *16*:387, Part I (March) 1957.
2. Macy, I. E.; Kelly, H. J., and Sloan, R. E.: The Composition of Milks, Publication 254, Washington, National Research Council, rev. 1953, p. 66.
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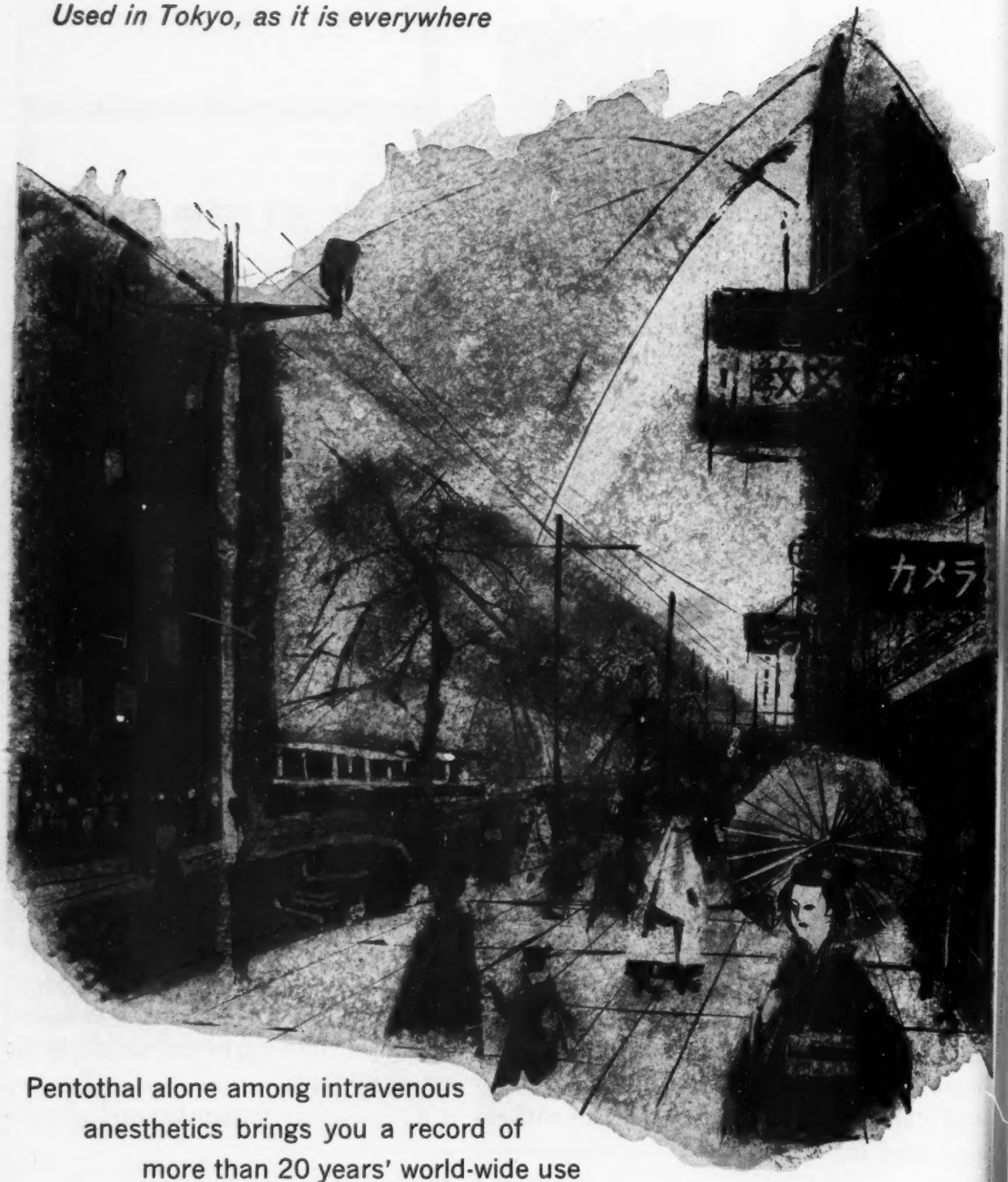

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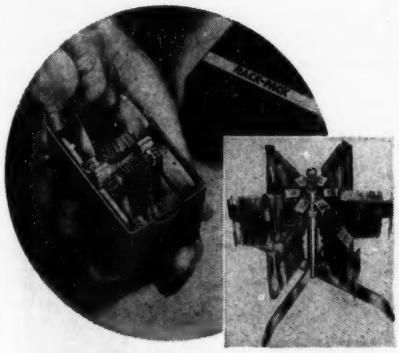

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References: 1. Obst. & Gynec. *1*:94 (Jan.) 1953. 2. Illinois M. J. *105*:305 (June) 1954. 3. Bull. Margaret Hague Maternity Hosp. *6*:107 (Dec.) 1953. 4. Missouri Med. *51*:727 (Sept.) 1954. 5. J. Michigan M. Soc. *53*:862 (Aug.) 1954.

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Refer to Schering literature for specific information regarding dosage, side effects, precautions and contraindications.

TRILAFON Tablets: 2, 4 and 8 mg., bottles of 50 and 500.

(1) Compilation of investigative studies, Schering Corporation.
(2) Department of Pharmacology, Schering Corporation.
(3) Ayd, F. J., Jr.: J. Am. Geriatrics Soc. 5:92, 1957.

*T.M. TR-J-957

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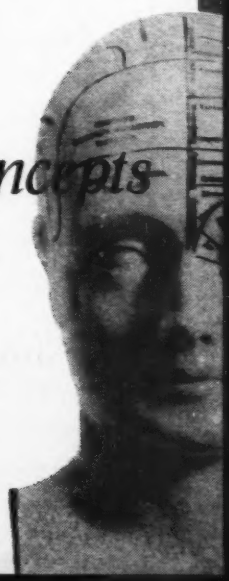

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1. McGoogan, L. S.: J. Michigan M. Soc. 55:68 (June) 1956.

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is patient's severe
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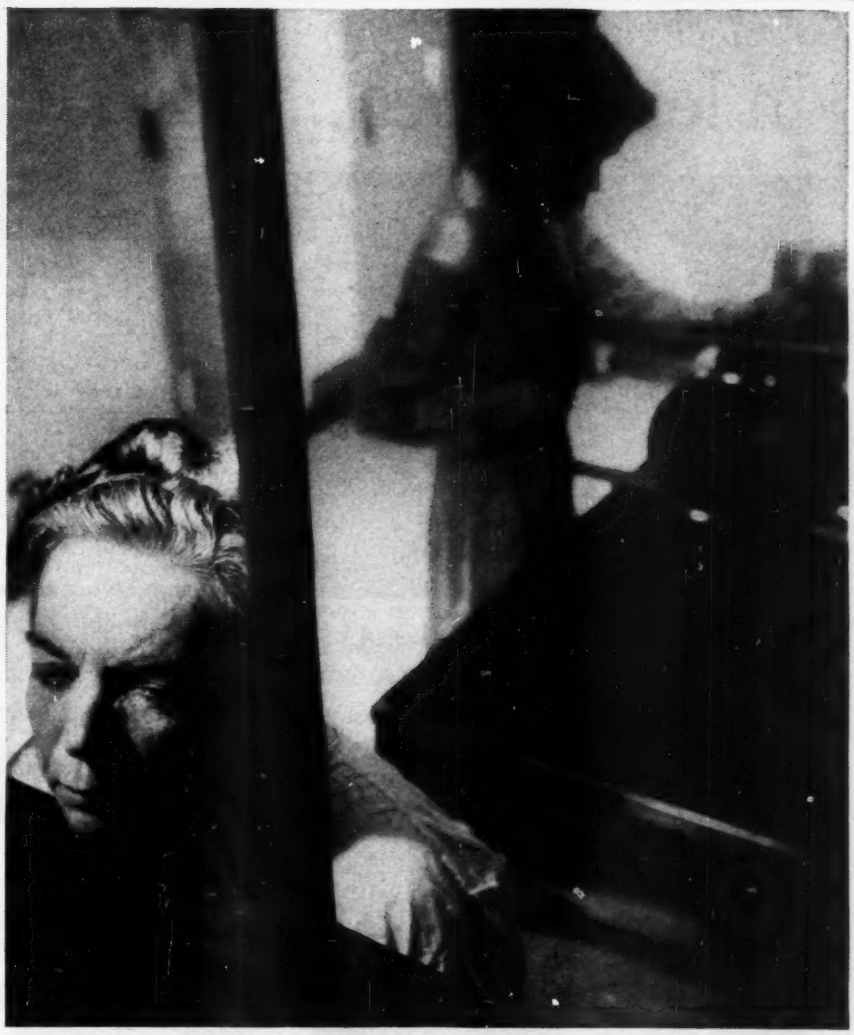

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patient: 60-year-old female. After death of relative from cancer, patient developed severe epigastric pain, was convinced pain was due to hidden malignancy which defied the X-ray. Her pain was unresponsive to antispasmodics. Her severe cancerphobia was untouched by sedatives and she refused psychotherapy.

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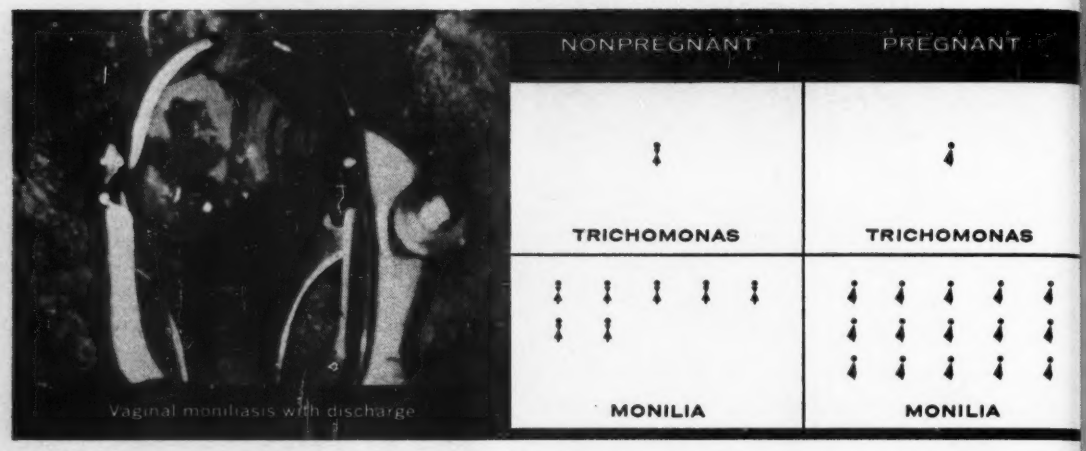
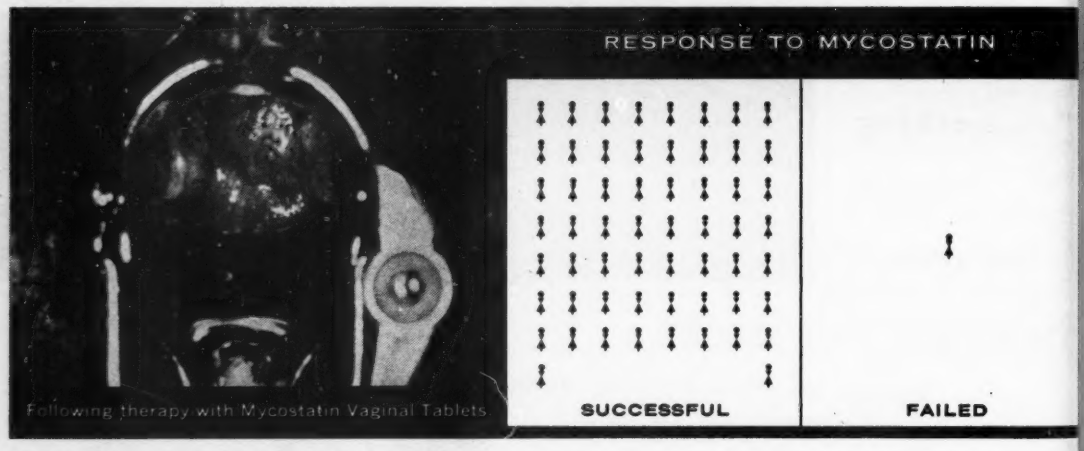
in leukorrhea...vaginal pruritus



In a current study of 76 unselected cases of vaginal discharge and pruritus, monilial vaginitis was *seven times* more common than trichomonal vaginitis in nonpregnant patients and *fifteen times* more common in pregnant patients.*



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*Pace, H. R., and Schantz, S. I.: J.A.M.A. 162:268, Sept. 22, 1956.

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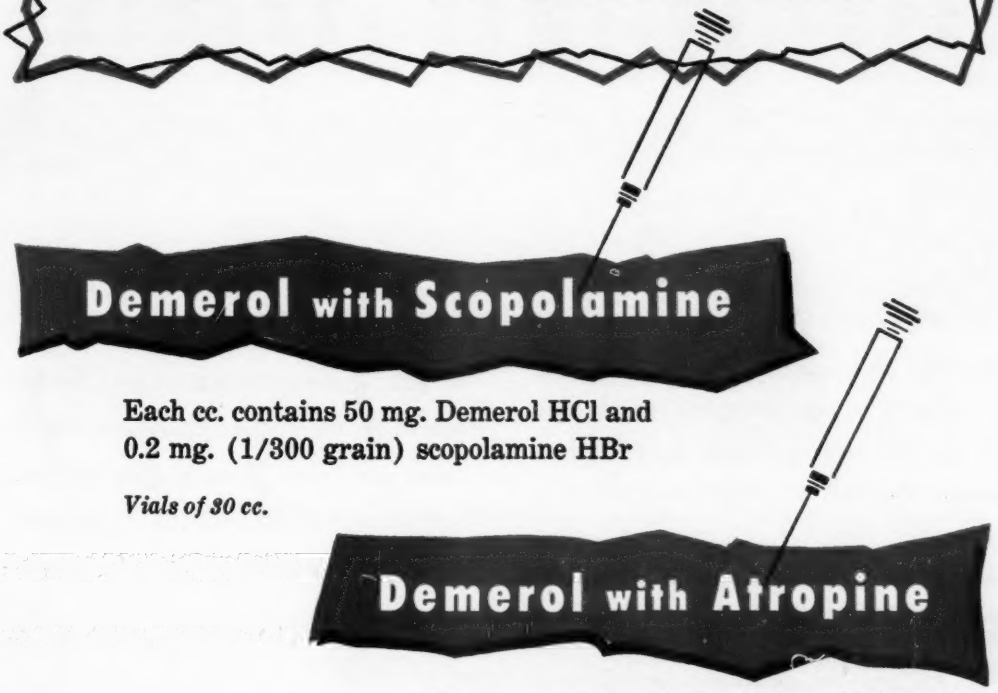

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ATLAS of CLINICAL ENDOCRINOLOGY

Covering Diagnosis and Treatmen

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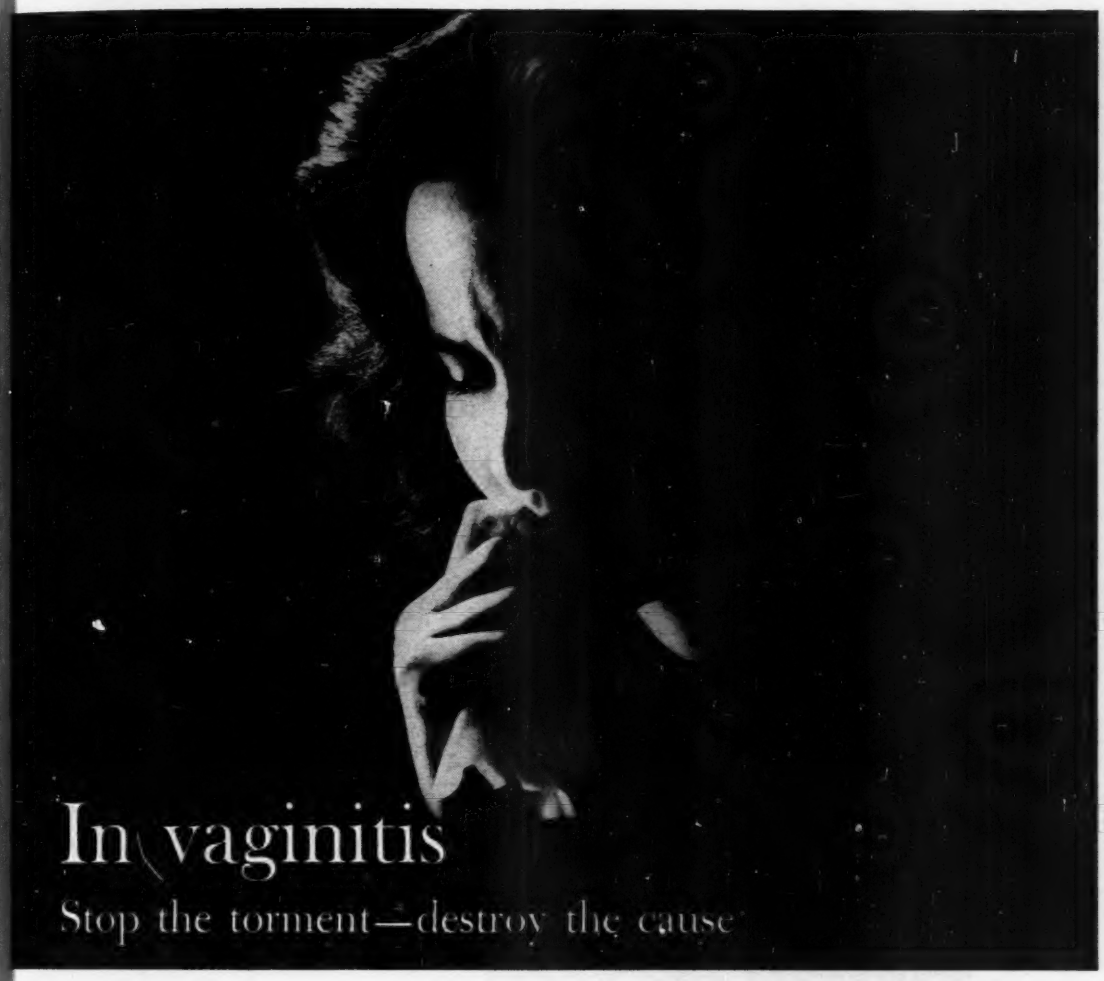

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Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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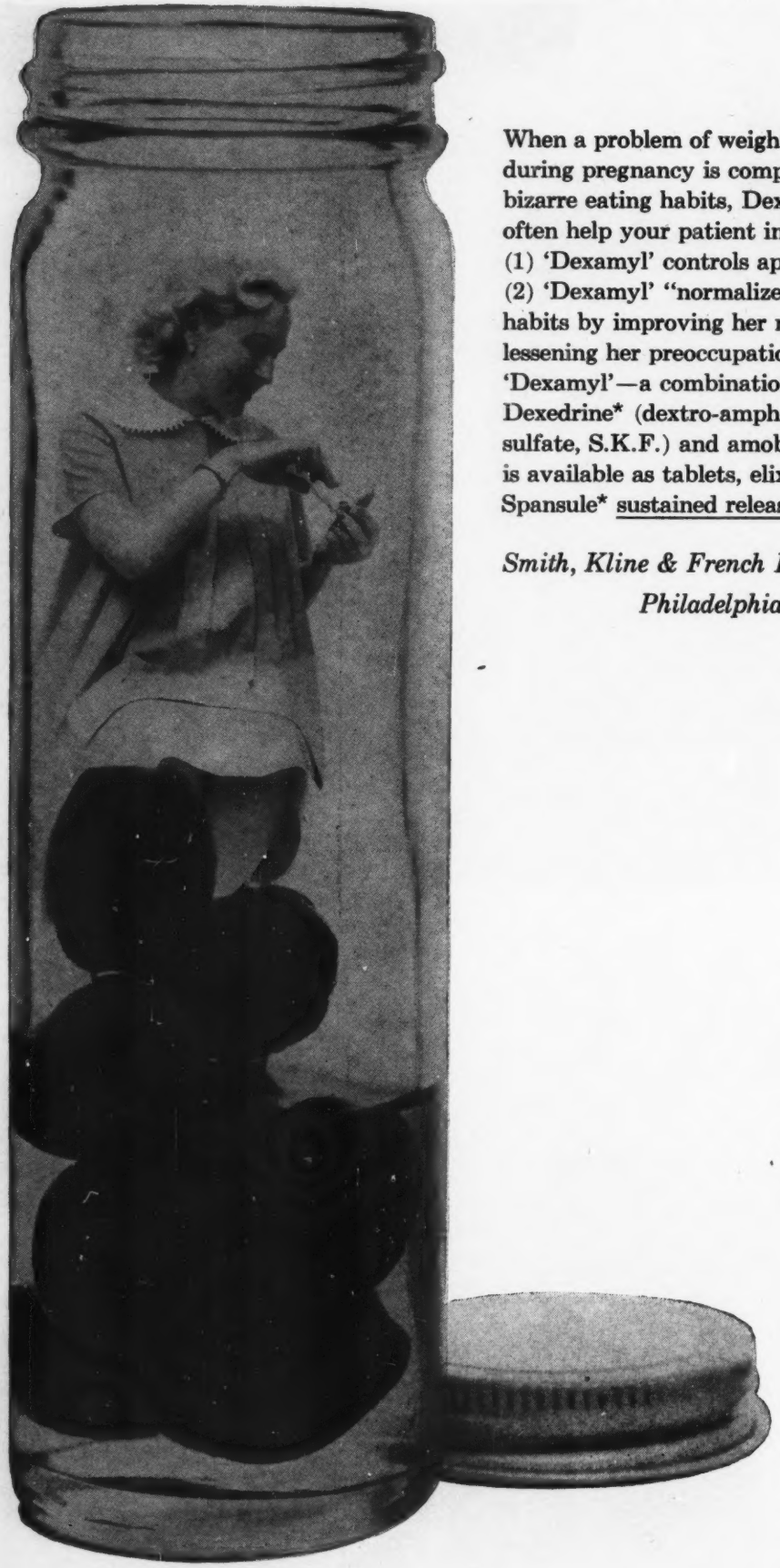

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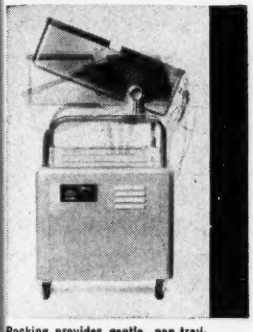

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References: (1) Millen, R. S.: N.Y. State J. Med. 55:779, 1955.
(2) Karpovitch, P.: Adventures in Artificial Respiration, New York, Associated Press, 1953.
(3) Eve, F. C.: Lancet 2:995 (1932); Eve, F. C., and Forsyth, N. C.: Brit. M. J. 2:554 (1948).

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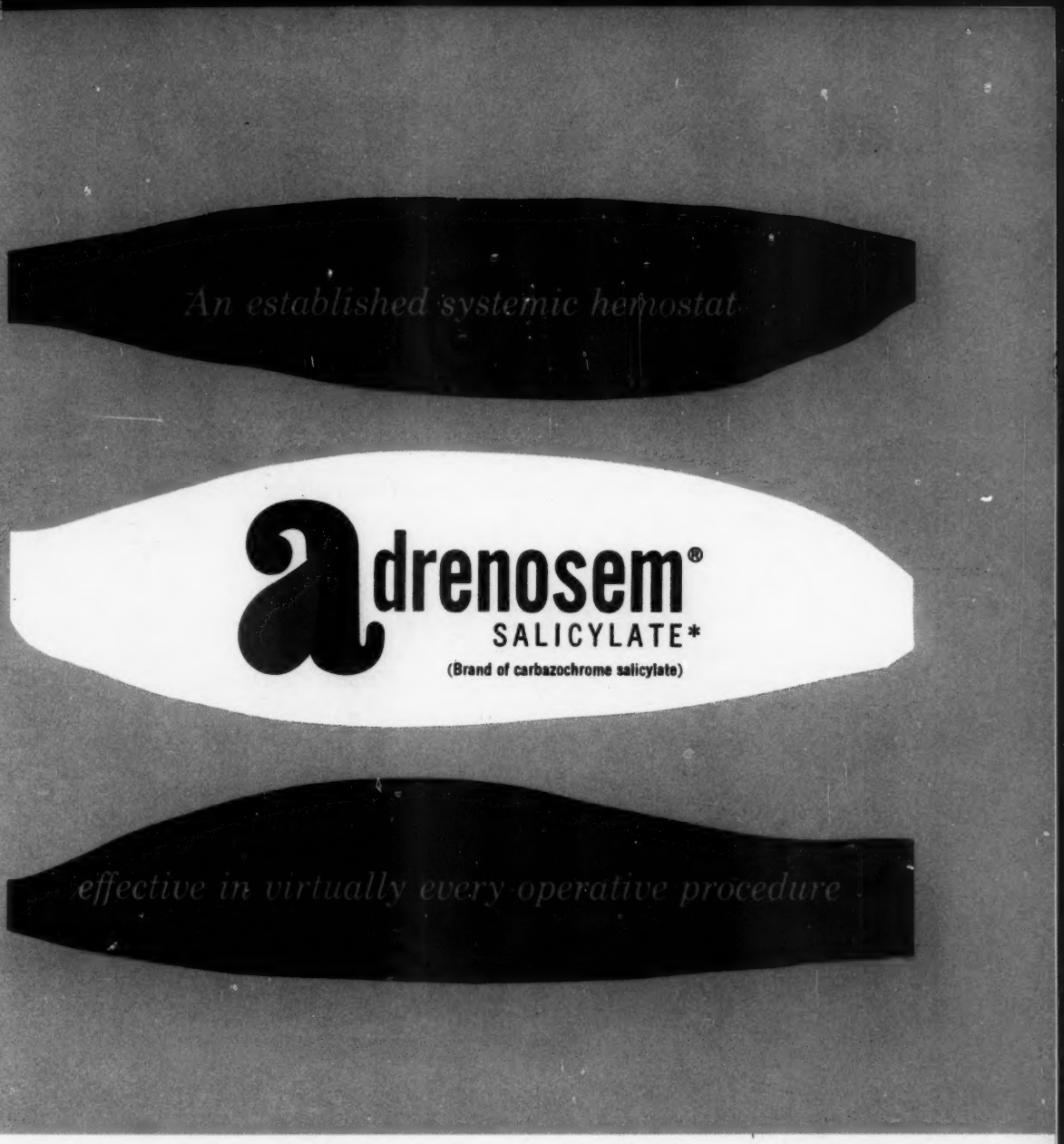

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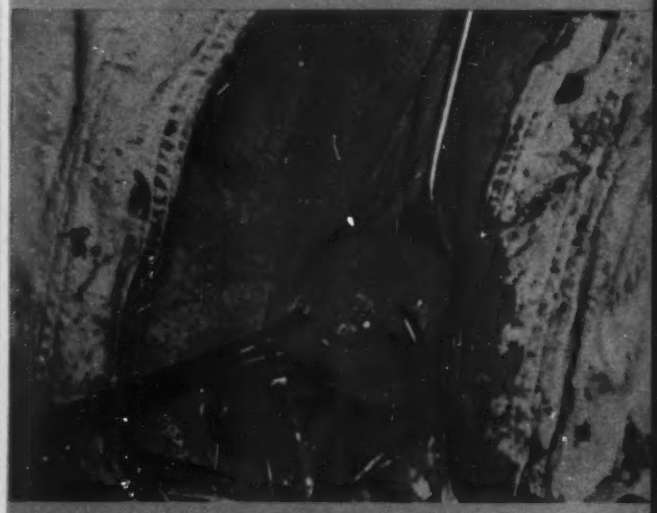

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1. Sadove, M.S.: J.A.M.A. *162*:712 (Oct. 20) 1956. 2. Lundy, J.S.: J.A.M.A. *162*:97 (Sept. 8) 1956. 3. Carroll, J.S., and Hudson, P.W.: Canad. Anaes. Soc. J. *2*:340 (Oct.) 1955.

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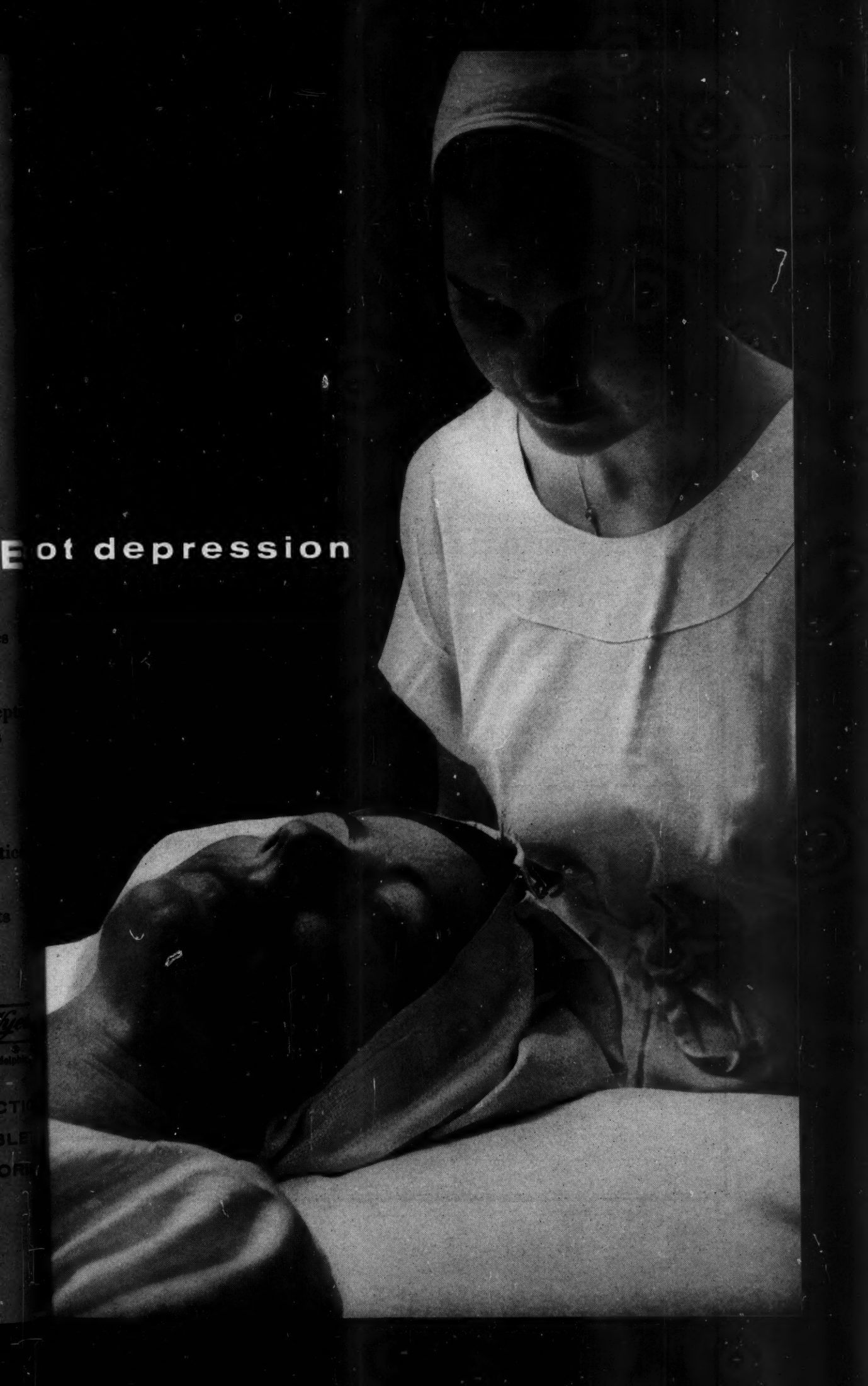
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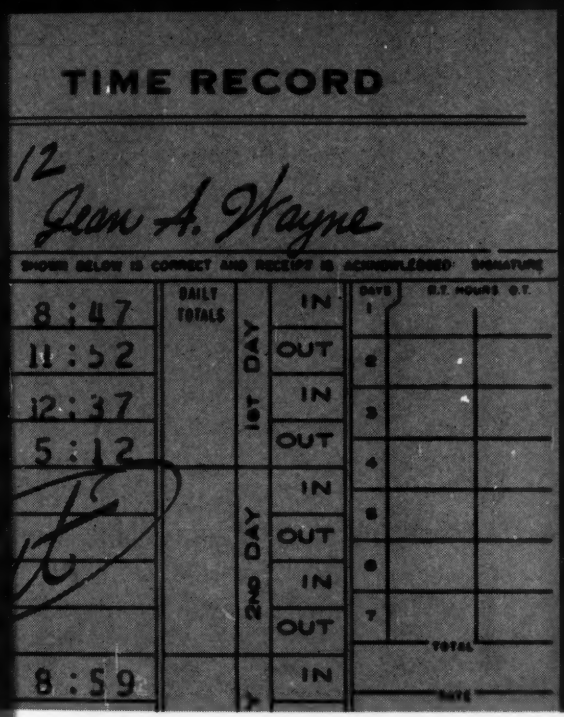

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INTRAVAGINAL MEASUREMENT OF RADIATION DOSE INCIDENT TO X-RAY PELVIMETRY AND HYSTEROSALPINGOGRAPHY

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DURING the past half century since the discovery of x-rays by Roentgen in 1895, diagnostic and therapeutic radiation has been used with increasing frequency in most branches of medicine. The diagnostic use of x-ray in gynecology and obstetrics has not been as extensive as in other fields. However, two specific procedures, x-ray pelvimetry and hysterosalpingography, have earned recognition as diagnostic aids in the practice of obstetrics and gynecology. One of the arguments advanced against the use of x-ray in obstetrics and gynecology is that the radiation may be harmful to the maternal ovaries and to the fetus. Even though no factual data have been presented to prove that *diagnostic roentgenology properly carried out* has produced damage of somatic tissues in the female, there is an implied hazard to the offspring of future generations through germinal changes.

Since the recent advances in the knowledge of radiation effects brought about by the development of atomic power, increasing attention has been directed to the measurement of actual radiation produced and delivered to the body. Measurements have been made by the use of phantoms, and estimations have been made of the dosage received at different depths in the body.

Investigations with flies, mice, and other organisms have been conducted to detect tissue damages and genetic effects.

The purpose of this communication is to record actual measurements in roentgens of radiation dosage directed to the depths of the female pelvis during the exposure of films for x-ray pelvimetry and hysterosalpingography. Measurements of x-ray dosage in 28 women subjected to pelvimetry or hysterosalpingography are presented, and an attempt is made to evaluate the nature of the risk involved, including the genetic implications. It may be noted that there is a marked paucity of information concerning the intrapelvic radiation dose as measured in the living patient.

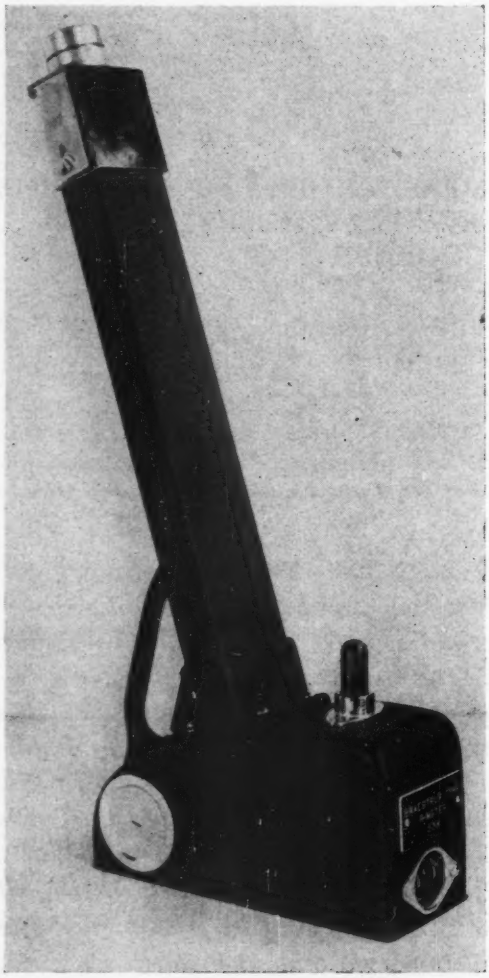

Fig. 1.—Electrometer. The 1 r ionization chamber is shown in the electrometer. (From Berman.[1])

The Measuring Instruments and the X-ray Equipment

The measuring instruments were designed by Braestrup and specifically calibrated for the pertinent radiation quality range to be employed in pelvimetry and hysterosalpingography. They consist of an electrometer (Fig. 1) and

three interchangeable ionization chambers (1 r, 5 r, and 25 r) (Fig. 2) with a plastic air wall, each with its own value per scale division. A specially devised close-sealing attachment or handle to the 1 r and 5 r ionization chambers permitted their insertion into the posterior vaginal fornix during the exposure of the films. The instruments were calibrated with no deviations prior to and following the series of measurements reported.

The x-ray apparatus was operated at 50 Ma. with an aluminum filter of 0.5 mm. thickness. The kilovoltage was variable from 60 to 85, depending upon the girth or thickness of the pelvis, as measured in centimeters.

The half-value layer was 1.2 mm. Al. at 85 kv., 50 Ma., and 0.5 mm. aluminum filter as calibrated by the Braestrup physicists. This apparatus was utilized for many years solely for diagnostic studies in obstetrics and gynecology. The factors of exposure and the technique of positioning have been standardized so that the roentgenograms show proper diagnostic quality and reproducibility.

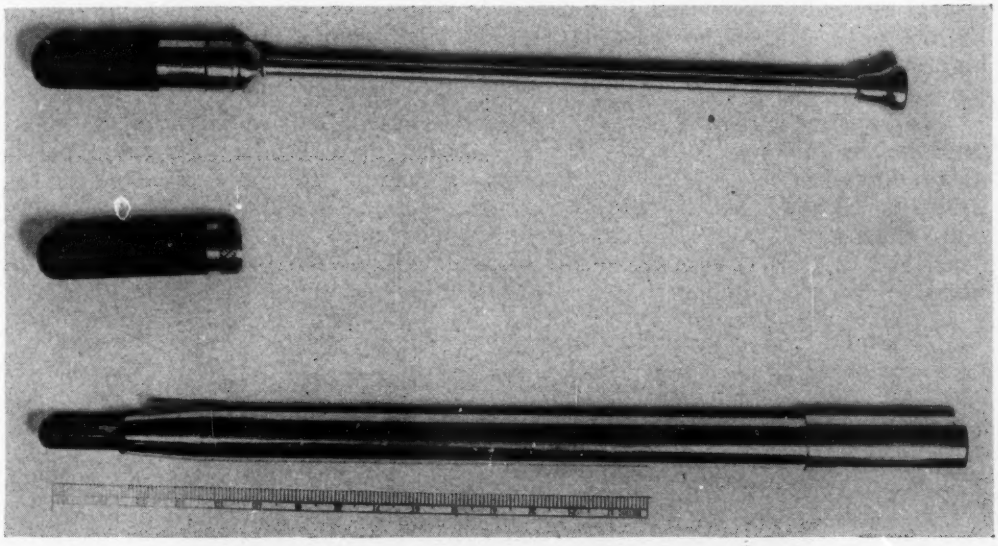

Fig. 2.—Ionization chambers. The chambers of 1 r, 5 r, and 25 r capacity are shown. A long metal handle is attached to the plastic chamber to permit its insertion into the vagina. (From Berman.[1])

The exposure factors determine the amount of radiation or dosage directed to the part under consideration, and they also determine the quality of the film. There is no agreement as to what constitutes a film of good quality. There is also no agreement as to the number and size of the films to be taken so that dosage will vary with the personal equation. Furthermore, it is probable that many x-ray installations are not calibrated. This means that in order to evaluate and to compare measurements of diagnostic x-ray dosage, it is necessary to know the factors of exposure, the number of films taken, the calibration of the x-ray equipment, and the means used to measure the radiation dose.

X-ray Pelvimetry

Measurements of x-ray dosage during pelvimetric studies were made in 13 women whose age averaged 30 years. The technique[1] involves the preparation of four films of the different pelvic aspects, taken at or near 38 weeks' gestation. The positioning of the patient, x-ray tube, and film, together with the exposure factors, are as follows:

1. Lateral View.—The patient stands in the true lateral position, or the lateral recumbent position may be used, if preferred. The tube-to-film distance is 37 inches (90 cm.), kv. 75 to 85, Ma. 50, exposure 9 seconds. The central ray is focused over the greater trochanter of the femur. The 5 r ionization chamber is inserted into the vagina posterior to the cervix (Fig. 3).

2. Inlet View.—The patient lies in the supine position with the upper back elevated on an inclined plane of 25 degrees. The tube-to-film distance is 37 inches (90 cm.), kv. 70 to 80, Ma. 50, exposure 6 seconds. The 1 r chamber is placed in the vagina (Fig. 4).

3. Outlet View.—The patient lies in the supine position. The tube is rotated to a 45 degree angle cephalad, and it is placed at a point 13 inches caudad to the symphysis. The central ray is thus directed approximately at right angles to the plane of the subpubic arch. In this position the tube-to-film distance is roughly 25 inches (60 cm.), kv. 65 to 75, Ma. 50, exposure 4 seconds. The 1 r chamber is placed in the vagina (Fig. 5).

4. Lateral View of the Uterus.—The patient lies either in right or left lateral recumbent position. The tube-to-film distance is 37 inches (90 cm.), kv. 60 to 70, Ma. 50, exposure 4 seconds. The central ray is directed to the highest point of the uterus, which is near the umbilicus. The 1 r chamber is placed in the vagina (Fig. 6).

Intrapelvic Dose.—The total intrapelvic dose of x-ray radiation, as measured in the posterior vaginal fornix in 10 patients exposed for the 4 pelvic views described previously, is indicated in Table I. The average dose for the group is 2.9 r, with 6 patients receiving less than 3 r and but one receiving more than 4 r. Thus, with the x-ray exposures and the positioning previously described, 2 to 4 r were delivered to the depths of the pelvis during a full series of x-ray pelvimetry study of 4 films.

TABLE I. X-RAY PELVIMETRY. MEASURED TOTAL INTRAVAGINAL DOSE PER PATIENT

FILMS	ROENTGENOGRAMS
4	2.1
4	2.2
4	2.5
4	2.6
4	2.7
4	2.8
4	3.1
4	3.4
4	3.8
4	4.4
Average dose per patient	2.9 r

The ionization chamber was removed after each film exposure in order to measure the dose delivered during that specific exposure. The individual readings were added together to obtain the total dosage received during the entire pelvimetry study. In 3 patients of similar weight and girth, the 5 r ionization chamber was left in the vagina during the entire time required for the exposure of the 4 films (10 minutes). The cumulative intravaginal dose for each of these 3 cases is presented in Table II. There is close agreement showing totals of 2.1 r, 2.2 r, and 2.7 r.

TABLE II. X-RAY PELVIMETRY. CUMULATIVE INTRAVAGINAL DOSE PER PATIENT

CASE	AGE	WEEKS' GESTATION	GIRTH (CM.)	MINUTES	FILMS	ROENTGENS
A	21	38	29	11	4	2.1
B	27	38	33	10	4	2.2
C	29	38	32	10	4	2.7

Fig. 3.

Fig. 4.

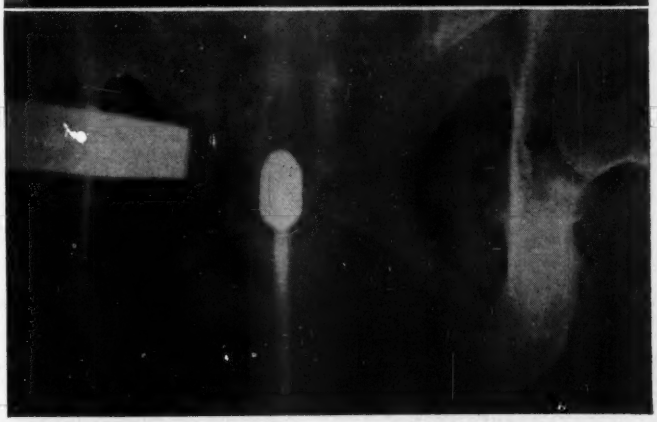

Fig. 5.

Fig. 3.—X-ray pelvimetry, lateral view. The 5 r ionization chamber is noted in the posterior vaginal fornix below the vertex. The chamber and the fetal head are both in the direct path of the central ray.

Fig. 4.—X-ray pelvimetry, inlet view. The 1 r ionization chamber is noted in the posterior fornix of the vagina. It lies in the direct path of the central ray. (From Berman.[1])

Fig. 5.—X-ray pelvimetry, outlet view. The 1 r ionization chamber is noted in the posterior vaginal fornix. The 25 r chamber is also shown in its position at the skin surface. It measures the dose received at the skin.

With respect to each of the 4 projections utilized in the pelvimetry studies herewith reported, the range of dose and the average dose recorded for each projection are as follows:

1. *Lateral:* range from 1.0 r to 1.7 r, average 1.4 r.
2. *Inlet:* range from 0.4 r to 1.1 r, average 0.5 r.
3. *Outlet:* range from 0.5 r to 1.1 r, average 0.7 r.
4. *Uterine:* range from 0.3 r to 0.6 r, average 0.4 r.

It is to be noted that the intravaginal dosage during the lateral film exposure amounts to almost half of the total dose for the entire series.

Fig. 6.—Uterus, lateral view. The 1 r ionization chamber which is placed in the vagina cannot be visualized in this view because it is obscured by the dense bones of the pelvis. The chamber lies outside the direct beam and it measures the oblique radiations together with the back scatter.

TABLE III. X-RAY PELVIMETRY. RECENT REPORTS

AUTHORS	YEAR	TOTAL ROENTGENS	FILMS	METHOD
Möbius[2]	1951	1.4	3	Intrarectal measurement
Ritter and others[3]	1952	3.6	3	Air dose, estimate
Stanford and Vance[4]	1955	1.1	2	Skin dose, phantom, estimate
Berman[1] and Sonnenblick[6]		2.9	4	Intravaginal measurement

Recently reported intrapelvic measurements or estimates made by others[2-4] interested in pelvimetric dosages are presented in Table III. In the second column of the table are noted the total doses in roentgens. The third column brings out some differences in the number of films taken and in the site and

methods of measurement made by different investigators. The dosage in roentgens as recorded by others for the lateral pelvic view is shown in Table IV.

TABLE IV. X-RAY PELVIMETRY. LATERAL VIEW

AUTHORS	YEAR	ROENTGENS	KV.	MA. (SECONDS)
Möbius[2]	1951	0.96	81-84	450-500
Ritter and others[3]	1952	2.91	78	780.0
Stanford and Vance[4]	1955	0.84	120	100.0
Berman[1] and Sonnenblick[6]		1.40	80-85	450.0

Hysterosalpingography

In hysterosalpingography a variable number of x-ray films are taken for the purpose of visualizing the Fallopian tubes and also the uterine cavity.

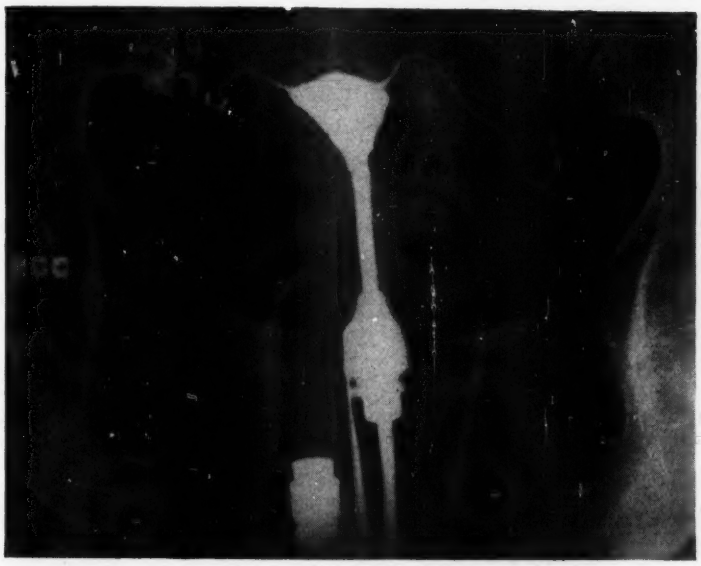

Fig. 7.—Hysterosalpingography. The 1 r ionization chamber is noted adjacent to and posterior to the cervix. The exposure was made after the injection of 2 c.c. of contrast substance.

The patient lies in the supine position in the modified lithotomy position. A 10 c.c. syringe attached to a self-retaining Jarcho uterine cannula is used for the injection of the contrast substance, which may be either the water-soluble or the oily type. A preliminary or scout film is taken before the injection, and 5 to 7 films are exposed after the injection of known amounts of contrast substance. Small amounts of 1 to 2 c.c. are used. The exposure factors are as follows: tube-to-film distance 30 inches (76 cm.), kv. 55 to 65, Ma. 50, exposure 4 seconds. The central ray is focused over the uterine cavity which is usually located just above the symphysis. A tenaculum on the anterior lip of the cervix permits gentle traction to straighten the uterine cavity.

The 1 r ionization chamber is placed in the posterior vaginal fornix in most patients (Fig. 7). In some instances it must be inserted anteriorly or laterally to the cervix depending upon the space available. The size and shape

of the vagina, the size and position of the cervix, and the space occupied by the instruments will determine where the ionization chamber must be placed.

Intravaginal Dose.—The range of the total measured roentgen dosage within the depths of the pelvis is shown in Table V. Twelve patients were given 5, 6, or 7 x-ray exposures. The total dosage varied from a low of 2.5 r (5 films) to a high of 4.5 r (7 films). The average intravaginal dose for each individual film was 0.6 roentgen. The average of the total dose to the pelvis was 3.5 roentgens. It appears that the total dose is roughly proportional to the number of films taken. The important measurement in hysterosalpingography is the average dose per film utilizing the technique and the factors of exposure as herewith described.

TABLE V. HYSTEROSALPINGOGRAPHY. MEASURED TOTAL INTRAVAGINAL DOSE PER PATIENT

FILMS	ROENTGENS
5	2.5
5	2.9
5	3.7
5	3.8
6	2.9
6	3.1
6	3.5
6	3.7
6	4.0
6	4.2
7	3.3
7	4.5
Average dose per patient	3.5 r

As in the pelvimetry studies, the ionization chamber employed was removed from the vagina after each exposure in order to measure the dose for each film. However, in 3 women of similar weight and girth, the 5 r chamber was left in the vagina for the entire exposure of 6 films and the cumulative dose was then recorded for the entire hysterosalpingography as noted in Table VI. The cumulative doses for the 3 cases are 2.9 r, 3.1 r, and 3.5 r, which is in good agreement considering the complex of variables involved in such measurements. The x-ray dose for each film as measured in this cumulative manner is 0.5 r as compared with 0.6 r obtained when each film is measured individually.

TABLE VI. HYSTEROSALPINGOGRAPHY. CUMULATIVE INTRAVAGINAL DOSE PER PATIENT

FILMS	ROENTGENS
6	2.9
6	3.1
6	3.5
Average dose per patient	3.2 r

In hysterosalpingography, the important consideration is the radiation dose received by the ovaries. Some reports of the ovarian dose have been based on estimations from phantom studies and estimations from the skin dosage. There are strikingly few reported measurements of the intrapelvic

dose in the living patient during hysterosalpingography. It has been stated by Stanford and others[5] in 1952 that of 20 different diagnostic x-ray procedures the mean gonad dose was highest in hysterosalpingography, with a reported figure of 27 roentgens. This estimate is much higher than the measurements reported in this communication. In the light of the disparity, additional studies with adequate controls of procedure and instrumentation might be made by others to provide more knowledge of the range of dose during hysterosalpingography.

Fluoroscopic control during hysterosalpingography is widely used because it offers the advantage of visualizing the filling of the uterus and tubes. It also aids in detecting errors in technique and extrauterine infiltration of the contrast substance. In this study, fluoroscopy was not utilized because the fractional injection of very small amounts of contrast and the immediate development of each film provides similar advantages. There is no desire to minimize the value of fluoroscopy during hysterosalpingography. However, it must be pointed out that the amount of radiation directed to the pelvis and particularly to the ovaries is inevitably increased during fluoroscopy.

Individual spot films must also be taken even if fluoroscopy is used. The time used during fluoroscopy serves to increase the amount of radiation as compared with single films taken by the fractional method. There is apt to be inadequate realization of the time consumed and the roentgen output during fluoroscopy. In addition to the increased radiation received by the patient, the radiologist who controls the fluoroscopy and the gynecologist who injects the contrast substance are subjected to radiation resulting from back scatter and possibly inadequate protection. If hysterosalpingography is performed frequently, the cumulative effects of the scattered radiation may be damaging to the operators.

Comment

It is recognized that all ionizing radiation, no matter how small the dose may be, is undesirable and potentially harmful to human tissues. The degree of such harm must be weighed against the value derived from the use of the x-ray for diagnosis and therapy. In diagnostic roentgenology the exposure factors which are used for each film should be selected so that the least amount of radiation necessary to yield a film of high quality will be utilized.

With the technique as described in this report, the total intrapelvic x-ray dose during pelvimetry or hysterosalpingography ranges between 2 and 4 r. It is possible that changes in the radiological factors such as added filtration, higher kilovoltage, faster films, or other technical improvements could diminish the amount of radiation and still produce a film of good diagnostic quality. Indeed, Stanford and Vance in 1955 studied such variations of technique in many diagnostic procedures, but, unfortunately, hysterosalpingography was not included. They suggested that the best approach to diminishing radiation dosage is to reduce the number of films and to reduce the size of the field exposed. It is probable that other investigators, by using different factors of exposure and varying the number of films, may obtain marked

differences in measurements of radiation. The direct value which can be derived from such reports lies in the standardization of the technique of pelvimetry and hysterosalpingography with proper consideration of the *intrapelvic dosage* rather than diagnostic quality alone.

Dosage to the Ovaries.—Can the published estimates of x-ray dose, received either in the vagina or in the rectum during diagnostic studies, be considered as the true dose to the ovaries? It is not possible, in the living subject, to place the ionization chamber in direct contact with the ovary. The dosage may be different to each ovary depending upon how close the measuring chamber is to the gonad.

It must be pointed out that there is a difference in interpretation of ovarian dosage in pelvimetry studies and in hysterosalpingography. During pregnancy the maternal ovaries near term are carried out of the pelvic cavity and displaced laterally by the enlargement of the uterus. This situation is clearly noted at the time of cesarean section. It is probable that the ovaries are not in the direct line of the x-ray beam and that the ovarian dose therefore is much less than the measured intravaginal dose. This applies particularly in the inlet and outlet pelvic views, since the ovaries are at some distance from the central ray. In the lateral pelvic view one ovary is at a higher level than the other and hence the dose received by each ovary will be different. However, even in the lateral view the gonads are not in the central ray, so that the intravaginal dose may be considered to be maximal. There is no direct method of measuring the dose to the ovary in the living patient except by the consideration of factors such as the quality of the incident radiation and depth dosage estimations. The ovaries also have greater protection from the surrounding pelvic structures, as compared with the relatively unprotected ionization chamber situated in the vaginal cavity.

As far as the fetal ovaries are concerned, it is possible at this time merely to speculate as to dosage. The presentation of the fetus determines the location of the gonads in relation to the x-ray beam. In breech presentations, the gonadal dose will be greater theoretically than in cephalic presentations. Since the fetus lies protected in the uterine cavity, the incident radiation to it is likely to be reduced. The total body irradiation of the fetus must also be considered, but at present there are no means for such measurement. Since the fetus is a large organism as compared with the ovaries, only partial body exposures occur during pelvimetry. The x-ray beam is directed to different portions of the fetus in the various views. In the inlet and lateral films, the fetal head lies in the central ray, and since the vertex lies closer to the tube than the ionization chamber, it is likely that the head receives a dose higher than that recorded in the posterior fornix. The fetus also receives scattered radiations from the uterine wall, amniotic fluid, and the maternal pelvic structures. This is true for all projections. In the lateral view of the uterus, the central beam is directed at the fetal thorax and abdomen which receive a

higher dose than that measured in the vagina. The fraction of the dose delivered to the fetal gonads cannot be estimated at this time, but that there is such a dose should not be overlooked.

In hysterosalpingography which is performed on nonpregnant women the ovaries are located in the depths of the pelvis in the vicinity of the posterior vaginal fornix. Therefore, the dose measured in the ionization chamber can be regarded as essentially that received by the ovaries. Since many of these women will subsequently become pregnant, the dose to their ovaries is an important consideration. Later, during pregnancy, x-ray pelvimetry may also be performed, thus adding more radiation to the gonads. In x-ray studies of the postmenopausal patient for abnormal bleeding, the radiation effects on the ovaries become of lesser importance, since these patients will not become pregnant.

Genetic Aspects.—It was appreciated very early in the use of x-ray that there was danger of tissue damage, particularly to the skin, blood, and gonads. It is believed also to affect the life span of the individual exposed to relatively large amounts of radiation. The effects on the gonads are particularly important because they may result in genetic alterations, many of which may be detrimental to progeny of the first or later generations.

There are two aspects involving the effects of radiation. The first deals with the individual only and it concerns itself with somatic tissue damage, particularly to the skin and blood. The second deals with changes in the germ plasm and therefore may affect the welfare of future populations. Because of the genetic implications which are concerned with the germ plasm of the population as a whole, the problem is one of public health. The germ plasm is the only link between the present and future generations. Therefore, the possibility of damage to the gonads by radiation has caused serious concern and misgivings, particularly among geneticists.[6] Even though there are large gaps in the knowledge concerning long-range radiation effects, there is evidence at hand that many heritable alterations of the germ cells (mutations) can result in some measure of impairment to succeeding generations.

The mutagenic effects of radiation on the germinal material of many nonhuman organisms, such as flies, viruses, plants, insects, and mammals, have been established by experimentation.[7, 8] One must be exceedingly cautious in directly applying the data and principles derived from animal investigations to the human. It must be noted, however, that there is no evidence which indicates that man has qualities of uniqueness in his response to penetrating radiation.

It is an accepted fact that the genetic effects of radiation are cumulative and that the total dose received during the reproductive lifetime of the individual has its full effect on the germ plasm. It is also important to emphasize that the entire dosage of radiation directed to the individual is derived from many sources, which include cosmic rays, natural sources, medical and dental x-rays, as well as fallout and waste materials from atomic power weapons and reactors. There is no question but that the radiation received by the general

population from all sources will increase in the near future. The important consideration is the per capita radiation level which is sufficient to produce serious genetic damage to future generations. At the present time there is no firm knowledge in regard to this radiation level.

Even though the use of x-ray is associated with a certain slight element of risk to the individual and to the future generations, a proper sense of proportion is necessary in weighing the relative hazards against the benefits to be derived from its use. It would be sheer folly to take the position that because of the potential hazards, the proper use of x-ray should be discouraged or eliminated. Any procedure in medicine and surgery entails certain calculated risks, not to mention the risks which are involved in the process of daily living.

Summary and Conclusions

1. Measurements of intravaginal radiation doses in the living patient are recorded for the procedures of x-ray pelvimetry and hysterosalpingography.

2. The instruments used for the measurement in roentgens of radiation dosage are described.

3. The total average intravaginal dose for x-ray pelvimetry (series of 4 films) is 2.9 r.

4. The total average intravaginal dose for hysterosalpingography (series of 6 films) is 3.2 r.

5. The dosage received by the fetus and the maternal ovaries during x-ray pelvimetry is discussed; the dosage received by the ovaries during hysterosalpingography is also discussed.

6. The genetic aspects of radiation dosage are discussed in brief in the light of the present knowledge.

7. X-ray equipment should be calibrated and the factors of x-ray exposure should be selected to reduce the amount of radiation to the minimum, consistent with quality films.

8. There should be no hesitation in utilizing indicated diagnostic procedures in obstetrics and gynecology, if the technique is properly carried out.

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SQUAMOUS-CELL CARCINOMA OF THE UTERINE CERVIX*

A Histochemical Review

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CHARACTERISTICS of squamous cells of the uterine cervix have received intensive study in recent years. The clinical importance of squamous-cell carcinoma of the cervix has given impetus to much of this investigation. Clinicians[40, 49] have welcomed new methods of study of cervical squamous cells and have participated in combined clinical and laboratory studies. This clinical interest greatly facilitated the development of exfoliative cytology and has intensified detailed morphologic study of tissue sections of the cervix.[44]

From a more abstract viewpoint, cervical squamous carcinoma has many attractions for the scientist interested in fundamental biologic research in cancer. Clinical material is abundant. The cervix sheds fascinating cells under conditions suitable for investigation. It is accessible to biopsy and to smear preparation. Therefore its physiology and pathology (including carcinoma) can be followed through natural evolution or through response to various treatments with an ease impossible in most tumors of internal organs. The cervix has interesting hormonal responses. It undergoes proliferative reactions during pregnancy in conjunction with the rapid growth of certain other portions of the generative tract.[39]

The comparatively simple cytoarchitecture of squamous epithelium of the cervix is another advantage in its consideration as a research tool in cancer investigation. The recognition of a malignant squamous cell is based on a group of straightforward characteristics, including nuclear-cytoplasmic ratio, nuclear hyperchromatism, and cytoplasmic basophilia.[45] Tissue architecture (or the positional relationships of cells) is of importance in the diagnosis of squamous-cell carcinoma. First, it is necessary in the determination of invasion.[8] It is also important in consideration of cell maturation.[46] The maturation of normal squamous mucosa is apparent in the regular progression of certain cell changes (e.g., diminishing nuclear-cytoplasmic ratio) from basal to superficial layers.[34] These changes are simple and easily evaluated when compared to maturation patterns in some other tissues and their tumors, as,

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for example, osteoid and osteogenic sarcoma. In certain types of microanalysis, including photomicrometry, it is possible to obtain a "pure" sample consisting only of the types of squamous cells under study. To illustrate this, put the high dry objective of the microscope on squamous mucosa, or on many examples of squamous-cell carcinoma. It is easy to find fields containing only squamous cells (nuclei and cytoplasm) with no fibrous tissue, blood, inflammatory cells, necrosis, secretion, or tissue spaces. Try next to obtain a similar field full only of the suspect tissue (one cell type only) in endometrial adenocarcinoma.

All of these considerations first attracted us to investigations of squamous-cell carcinoma of the uterine cervix in 1949. Since that time we have been attempting to bring new methods to this field of investigation. These methods have been originated by basic scientists, including anatomists,[52] histochemists,[42] and biophysicists.[2] Our approach has been to review new methods of cell study developed by these investigators, consider which might have relevance to growth in the human uterine cervix, make necessary adaptations, and design a research problem utilizing available material.

Our first essay was an attempt to apply quantitative methods to the study of specific chemical substances in exfoliated cells. In differential counts of cervical smears stained for glycogen[15] a significantly higher percentage of squamous cells contained glycogen in smears from pregnant as compared to those from nonpregnant women. A group of pregnant women receiving fairly large doses of diethylstilbestrol showed a *lower* percentage of glycogen-containing cells in cervical smears than did a control group.[16] Turning to photomicrometry[9] we found closely approximating estimated hyperchromatism in invasive squamous-cell carcinoma and intraepithelial carcinoma. This property of hyperchromatism in neoplastic epithelium differed markedly from that found in the same study in metaplastic epithelium or normal portio vaginalis mucosa. In a later study of planimetric quantitation of nuclear-cytoplasmic ratio,[10] again invasive and intraepithelial carcinoma showed nuclear measurement properties closely approximating each other. These differed markedly as regards "maturation index" from metaplastic or normal squamous epithelium. Atypical hyperplasia of the cervix[27] exhibited nuclear measurement properties lying somewhat between those of intraepithelial carcinoma and those of squamous metaplasia.

Utilizing the histochemical approach, we have investigated the distribution of succinic dehydrogenase, a vital respiratory cellular enzyme, in normal and neoplastic cervical epithelium. In a series of cervical biopsies from pregnant and nonpregnant women[18] sites of dehydrogenase activity corresponded well to sites of cellular proliferation as seen in conventional sections. The same technique was employed in a study of 15 cases of cervical carcinoma, and 37 cervices removed for other reasons.[20] Here dehydrogenase activity correlated closely with sites of growth in both normal and abnormal epithelium. Specific localization of succinic dehydrogenase and endogenous reductase[17] gave distribution patterns in normal and cancerous squamous epithelium corresponding to areas of apparent growth. Protein-bound sulfhydryl

groups, important in various phases of cell growth, were identified in normal, metaplastic, and carcinomatous squamous epithelium of the uterine cervix.[30] Disulfide groups were found in areas of intracellular keratinization, including epithelial pearls. In contrast to current belief[37] as to absence of glycogen in cervical carcinoma, glycogen was demonstrated in 13 of 23 examples of invasive squamous-cell carcinoma of the cervix[26] when a sensitive technique of fixation and staining was used. In all of these varied approaches, growing cells gave one set of reactions, maturing cells another. None of these techniques, however, demarcated carcinoma cells from proliferating cells in metaplasia or in the basal layers of normally maturing portio vaginalis mucosa.

In pursuance of our general concept, a series of examples of squamous-cell carcinoma of the cervix and other cervical tissue have been subjected to a battery of histochemical techniques. These, with the reasons for their employment, are:

1. Localization of sites of dehydrogenase activity. This enzyme activity has been said to correlate with sites of active cellular function, including growth.[41]

2. Localization of sites of phosphamidase activity. This enzyme has been found in greater abundance in certain tumors than in normal tissues of the same cell types.[38]

3. Localization of sites of alkaline phosphatase activity. This enzyme group is important in certain functions of many types of cells.[42]

4. Localization of protein-bound sulfhydryl and disulfide groups. Sulfhydryl groups are important in varied cell functions.[4] Disulfide groups are particularly associated with keratinization,[3] a specific cytochemical differentiating feature of squamous cells.

5. Localization of glycogen. Glycogen is found in maturing squamous cells of the portio vaginalis, but has been reported as absent in squamous-cell carcinoma of the cervix.[37]

6. Localization of lipids. Lipids are constituents of all normal tissues although in general they cannot be demonstrated by microchemical methods except in the "depots."[6] In some cell types fat may be demonstrable during states of deterioration when not normally discernible.

In the use of these techniques, squamous carcinoma cells manifested much the same histochemical reaction pattern as cells from the basal layers of nonneoplastic squamous mucosa. In general cytochemical evidence of differentiation paralleled cytomorphologic differentiation.

Materials and Methods

Seventy-two examples of squamous-cell carcinoma were studied. These came from 41 patients, some being repeat biopsies. Sixty-eight biopsies not disclosing carcinoma were studied for comparison. Most of these showed some squamous metaplasia and epidermidalization of glands. Five manifested some degree of atypical hyperplasia. There were varying degrees of cellular differentiation in the examples of squamous-cell carcinoma. These patients had all stages of spread of tumor.

A. *B.* *C.*

Fig. 1.—Invasive squamous-cell carcinoma of cervix. (×142; reduced ¼.)

A, Hematoxylin and eosin section.

B, Dehydrogenase localization. Formazan granules localizing sites of dehydrogenase activity are present in considerable concentration in the cytoplasm of neoplastic squamous cells. Adjacent fibrous tissue shows a much lesser degree of reaction.

C, Sudan black B technique. Faint staining of lipid localization is present in the cytoplasm of the carcinoma cells.

For localization of succinic dehydrogenase activity, biopsy blocks were incubated anaerobically for one hour at 37° C. in solutions containing 0.23 per cent neotetrazolium, 0.81 per cent sodium chloride, 0.03 M sodium succinate, and 0.09 M phosphate buffer, pH 7.4.[28] Control blocks were incubated in a similar solution except that 0.03 M sodium malonate was used instead of sodium succinate to inhibit succinic dehydrogenase activity.[43] Frozen sections (15 microns) were prepared.

Tissue blocks were fixed in ice-cold alcohol, 1 per cent trichloracetic acid in alcohol, Rossman's fluid,[52] and in neutral 10 per cent formalin. Sections (5 microns) from the alcohol-fixed blocks were processed to demonstrate alkaline phosphatase and phosphamidase.[33] Sections (5 microns) from the trichloracetic acid-alcohol-fixed blocks were processed to demonstrate protein-bound sulfhydryl and disulfide groups.[3] Disulfide groups were detected by treating sections overnight with 0.1 M sodium iodoacetate to block preexisting sulfhydryl groups and, after washing, by next immersing the slides in 10 per cent sodium acetate and 5 per cent sodium sulfite solution. After washing, the procedure for sulfhydryl localization was applied. Sections (5 microns) from the Rossman's-fluid-fixed tissues were subjected to the periodic acid-Schiff technique for the demonstration of glycogen.[35] Control sections were digested with malt diastase to remove glycogen. Frozen sections (15 microns) from the formalin-fixed blocks were stained with sudan black B (Bismarck brown counterstain) to demonstrate fat.[35]

Results

Since the sections were prepared from different tissue blocks, not all those from the same case showed comparable tissues. Some did not include carcinoma. The great majority exhibited relatively similar tissues in the blocks from a given case.

Sites of dehydrogenase activity were manifested in the tissue incubated in neotetrazolium by the deposition of black or brown formazan crystals and granules in the cytoplasm, or in certain instances by the presence of red microdroplets in the cells.[17] Control sections incubated in solutions containing malonate showed a much lesser degree of reaction. There was heavy cytoplasmic formazan deposition in endocervical glandular epithelium. Normally maturing portio vaginalis squamous epithelium revealed formazan deposition confined to the basal and immediately superjacent layers. Metaplastic squamous epithelium, whether on the surface or in glands (epidermidalization) showed a moderately diffuse deposition of formazan, usually more marked in the basal layer. Manifestation of dehydrogenase activity was found in varying degree in the neoplastic squamous cells (Fig. 1, *B*). In general, deposition of formazan was heaviest in the squamous carcinoma cells toward the periphery of a mass of tumor, and diminished progressively toward the center. No evidence of dehydrogenase activity was found in keratinized cells of epithelial pearls in well-differentiated carcinoma. In the stroma, moderate formazan deposition occurred about blood vessels and in the cytoplasm of inflammatory cells.

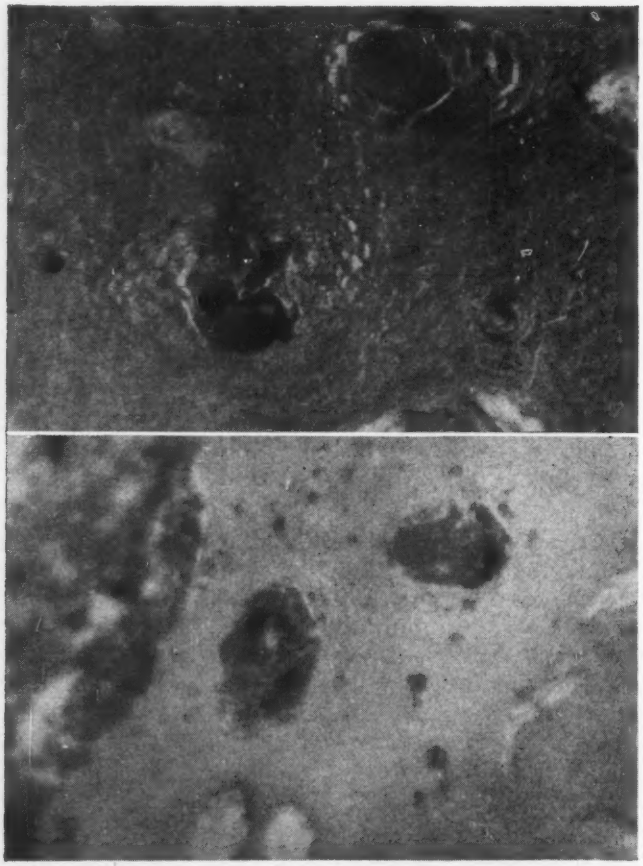
All of the squamous cells showed extremely faint cytoplasmic staining with sudan black B (Fig. 1, *C*). In regions of necrosis and keratinization, this was much more marked. Squamous epithelium, neoplastic or nonneoplastic, was much less sudanophilic than adjacent leukocytes.

All the squamous cells (neoplastic, metaplastic, and normal) showed moderate red-blue staining to the sulfhydryl technique, showing principally in nucleoli and cytoplasm. Epithelial pearls and regions of intracellular keratinization had a strong blue staining (Fig. 2, *A*). A considerable disulfide reaction was found in epithelial pearls and regions of intracellular keratinization (Fig. 2, *B*). Viable squamous cells in general had a weaker disulfide

staining than sulfhydryl staining. In most instances, however, disulfide reaction was found in all viable squamous cells. Nuclei of endocervical columnar cells had moderate sulfhydryl and faint disulfide staining.

Presumably valid alkaline phosphatase reaction was found in capillaries and in the cytoplasm at the tips of the endocervical columnar cells. Moderate

A.



B.

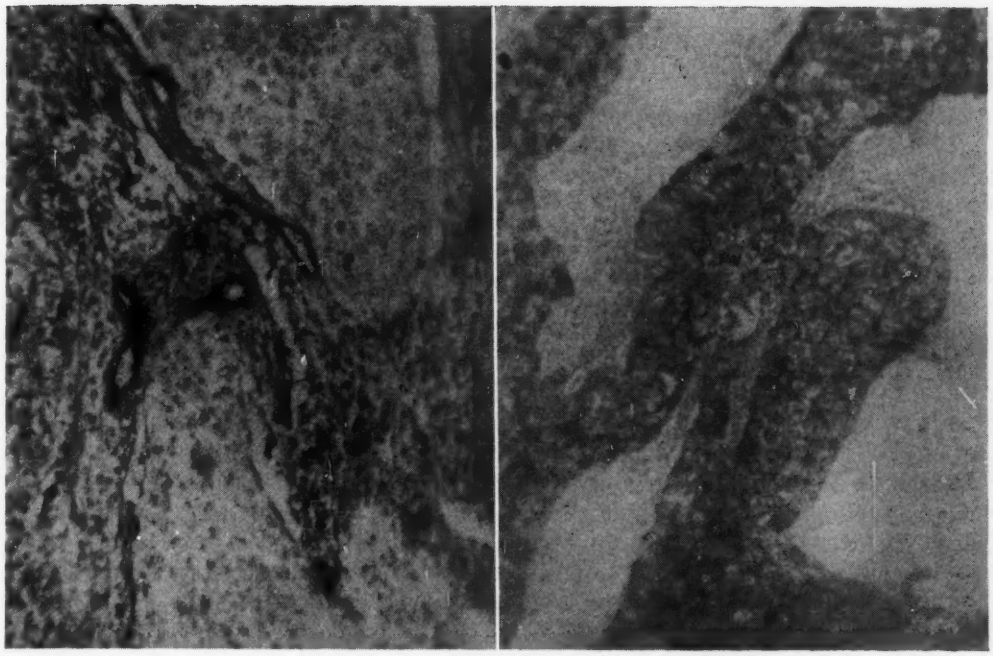
Fig. 2.—Invasive squamous-cell carcinoma of cervix with keratinization and epithelial pearl formation. (×142.)

A, Sulfhydryl-group technique. There is moderate cytoplasmic and nucleolar staining of the squamous cells. A considerably heavier reaction is present in the epithelial pearls and adjacent keratinizing cells.

B, Disulfide-group technique. Viable squamous cells show a very faint reaction, the staining of keratinized cells in epithelial pearls being comparatively heavy.

nuclear staining was found in columnar and in squamous epithelium, whether or not the latter was neoplastic (Fig. 3, *A*). However, this type of staining is now evaluated as an artifact.[42]

Moderate phosphamidase reaction occurred in the nuclei of endocervical glandular epithelium. Faint reaction was found in the cytoplasm at the tips of these cells. In normal portio vaginalis epithelium, phosphamidase reaction occurred principally in the basal layer, diminishing progressively in more superficial layers. The reaction for phosphamidase was seen principally in cytoplasm and in nuclear membranes with fainter staining of other nuclear

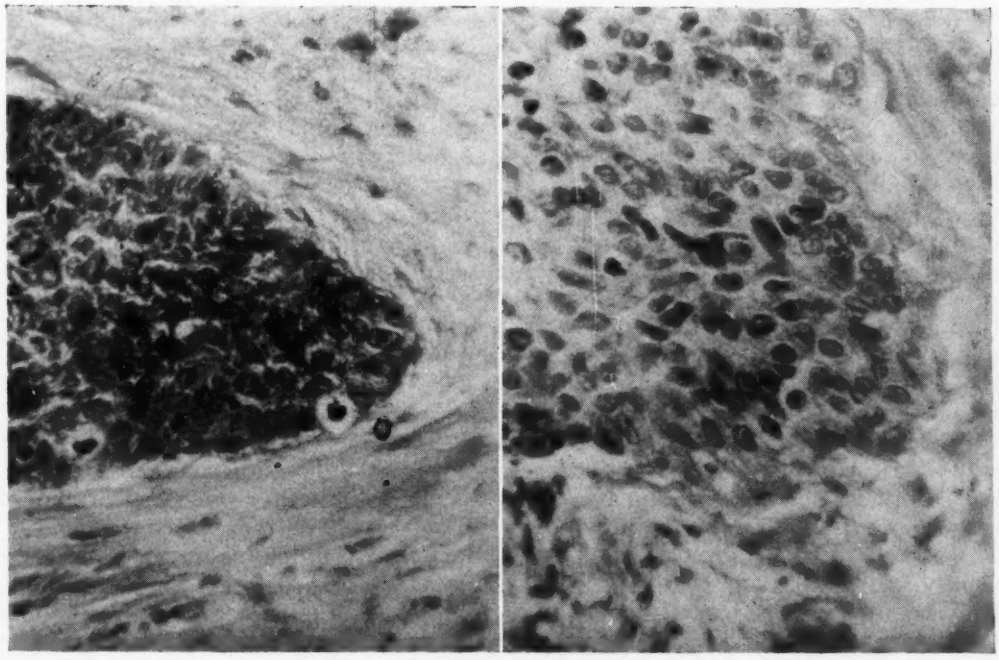


A. *B.*

Fig. 3.—Invasive squamous-cell carcinoma of cervix. (×142; reduced ¼.)

A, Alkaline phosphatase. No reaction is seen in the tumor cells except for slight staining of nuclei, which is evaluated as artifact. The endothelium of the capillaries reacts moderately.

B, Phosphamidase. A heavy reaction appears in the cytoplasm of tumor cells and much less in adjacent stroma.



A. *B.*

Fig. 4.—Invasive squamous-cell carcinoma of cervix. (×403; reduced ¼.)

A, Periodic acid-Schiff technique (hematoxylin counterstain). The dark-staining material in the cytoplasm of the tumor cells is presumably indicative of glycogen. Note the mitotic figures in the peripheral cell layers.

B, Periodic acid-Schiff technique (hematoxylin counterstain). This is from the same area depicted in Fig. 4, *A*, but this section has been subjected to malt-diastase digestion, which removes glycogen. This procedure proves the staining reaction in Fig. 4, *A*, to have been due to the presence of glycogen in the carcinoma cells.

structures. The carcinoma cells manifested a strong reaction of cytoplasm and of nuclear membrane to the phosphamidase technique (Fig. 3, *B*). Epithelial pearls had no reaction. Stroma and other components of the sections were little stained.

Heavy mucin staining was present in endocervical columnar epithelium. None of the squamous epithelial cells, whether neoplastic or nonneoplastic, showed material staining with the periodic acid-Schiff technique after malt diastase digestion. Because of the heavy mucin content, it is not possible to identify glycogen in the endocervical columnar epithelium.[51] Portio vaginalis squamous mucosa had no glycogen staining in the basal layer, but the intensity of glycogen staining increased with other evidences of maturation toward the surface. Similar but less-marked glycogen staining was found in metaplastic squamous epithelium. More than half of the examples of invasive squamous-cell carcinoma showed some glycogen staining of tumor cells. This was usually present toward the centers of neoplastic masses where other evidences of "maturation" occurred. Occasionally glycogen staining was seen in cellularly active areas, adjacent to cells in mitosis (Fig. 4).

Comment

The histochemical techniques employed in the current study relate to substances important in certain characteristics of squamous cells, or to cellular growth and metabolism more generally.

Succinic dehydrogenase is an important link in the chain of enzymes responsible for biological oxidation.[50] In the present material, as in previous studies,[17, 18, 20] sites of succinic dehydrogenase activity in cervical squamous-cell carcinoma corresponded generally with regions of growth, being absent in areas of keratinization. This correlation of dehydrogenase activity with sites of cell growth or active metabolism is supported by other investigations. We found such correlation in squamous-cell carcinoma of the skin,[28] as well as from oral mucosa, bronchus, vulva, and other loci.[12] This distribution pattern of succinic dehydrogenase in regions of growth is not peculiar to squamous-cell carcinoma. The enzyme is found in the basal layers of normally maturing cervical squamous mucosa[18, 20] and of normal epidermis.[29] Padykula[41] stated that the distribution pattern of this enzyme suggests that it is present in greatest concentration within those portions of tissues and organs that show metabolic capacity, or that are engaged in absorptive or secretory activity. Various studies support the thesis that this evidence of activity of the dehydrogenase enzyme group is a good index of general cell activity, whether neoplastic[7] or physiologic[22] growth, hormone secretion,[14, 23] exocrine secretion (as in endocervical glands),[18] or absorption (as in foreign body giant cells).[19] Diminution in histochemical evidence of dehydrogenase activity has been shown to be a good indication of cell damage, whether the effect of chemical substances upon the kidney[50] or irradiation on the placenta[24] or ovary.[21] The effects of irradiation upon the distribution of the dehydrogenase enzymes should be studied in squamous-cell carcinoma of the cervix. This no doubt would make a valuable contribution to our knowledge of cervical carcinoma. We have attempted to institute such a research program on two occasions, but problems of logistics have prevented our following a sufficient series through radiation therapy to warrant reporting.

We failed to demonstrate valid alkaline phosphatase in neoplastic or nonneoplastic squamous epithelium of the cervix. This enzyme is present only in slight amounts in the Malpighian layers of the epidermis[1] and is absent in

keratin. A considerable bulk of recent experimental work suggests that nuclear staining observed with the Gomori technique which we used is due entirely to artifact.[42] Using a more recently developed and probably more accurate technique, Wheeler and Danziger[51] found squamous epithelium of the portio vaginalis of the cervix to be unreactive. We[12] did not find valid cytoplasmic alkaline phosphatase reaction in examples of squamous-cell carcinoma from various noncervical loci.

Phosphamidase is thought to be an enzyme specific for hydrolyzing the bond between nitrogen and phosphoric acid in phosphoric acid-substituted amides.[38] Meyer and Weinmann found no phosphamidase reaction in normal oral mucosa. In the present study moderate reaction occurred in the basal layer of portio vaginalis mucosa. Meyer and Weinmann[38] reported that in general the amount of phosphamidase increased with increasing lack of cellular differentiation in a group of cases of epidermoid carcinoma of the oral cavity. The centers of horny pearls were negative in most instances, the peripheral obviously proliferating cells strongly positive. Our findings are much the same, except that the reaction occurred in all viable proliferating cells without particular correlation as to degree of differentiation. Phosphamidase has been has been localized in neoplastic and nonneoplastic epithelium of the breast[13] and in chondroblasts of chondrosarcoma,[25] among other loci. Gomori[32] observed large amounts of the enzyme in normal brain tissue and in malignant tumors of epithelial origin.

Sulfhydryl groups are important in different cell functions; in the coagulation of blood, in cell permeability, and in hormone synthesis and activity.[4] Sulfhydryl content of protozoa incre ed progressively during growth in experimental studies,[5] reaching a maximum before cell division. The sulfhydryl group content of tumor tissues in certain studies has been found greater than in nontumorous tissue. Normal epidermis contains in some of its layers a high concentration of sulfhydryl groups that can be detected by histochemical means.[48] As epidermal cells mature and keratinization develops, disulfide groups become more prominent. The sulfur of the epidermis and its derivatives is present mostly as cysteine residues in the Malpighian layer and cystine residues in the cornified layer.[31] At the limit between these two zones the sulfhydryl group of cysteine is oxidized to the disulfide bond of cystine, a process by which the keratin precursor present in the tonofibrils of the Malpighian layer is transformed into the completed keratin present in the tonofibrils of the cornified layer. Since sulfhydryl and disulfide groups provide an intracellular oxidation-reduction system in many tissues[3] it is not surprising to find keratinizing cells showing reaction to both. Our findings as regards distribution of sulfhydryl and disulfide groups in uterine cervical carcinomas in the present study are essentially similar to those we have previously reported in squamous-cell carcinoma of skin,[12, 28] bronchus, penis, vulva, nasal sinuses, and oral mucosa, as well as in a smaller group of cases of squamous-cell carcinoma of the cervix.[30]

We have discussed the significance of glycogen staining in invasive squamous-cell carcinoma of the cervix in more detail in a previous publication.[26] It has been our experience that a significant proportion of cases of squamous-cell carcinoma of the uterine cervix will show glycogen if sensitive methods of fixation and staining are employed. For this reason we are dubious concerning the value of glycogen staining as a *sine qua non* in the differentiation of squamous-cell carcinoma (intraepithelial or invasive) from nonneoplastic proliferative conformations of squamous epithelium. We have seen glycogen in squamous-cell carcinoma of Bartholin's gland[7] and vulva,[12] as well as from various other primary sites.

The significance of lipid (sudan black) staining of the present material is difficult to evaluate. Wheeler and Danziger[51] found sudanophilic particles in the cytoplasm of basal cells of portio vaginalis epithelium. Lipids, often in considerable reaction, were detected in parakeratotic and keratotic foci. In ordinary circumstances one rarely considers fat or fat staining in problems regarding squamous epithelium. It has been reported,[47] however, that there is almost as much lipid in the epidermis as there is protein. Conventional tissue techniques remove most of the lipid. Except as regards the ovary and its disorders,[36] lipids are little regarded in gynecologic pathology. Perhaps further attention to lipids would bring forth many points of interest.

Unfortunately the present series included no examples of intraepithelial carcinoma. As Wheeler and Danziger have indicated, the need for detailed anatomic study of suspected intraepithelial carcinoma to rule out invasive carcinoma must be paramount over basic research. Therefore a multiple block and fixation routine such as we employed could not be applied to cases of suspected intraepithelial carcinoma.

The reactions of the squamous cells in this study were not those of malignancy versus benignancy, but those of growth versus "maturation." Dehydrogenase and phosphamidase activity were found in proliferating cells, whether in the basal layer of normal mucosa, or in the peripheral portions of carcinomatous cell groups. Disulfide groups were found in areas of keratinization and glycogen in "maturing" cells, regardless of the biologic potential of the cells. Thus the outcome of our histochemical studies is much like that of our measurement investigations into nuclear size, nuclear-cytoplasmic ratio, and hyperchromatism.[9-11, 27] Growing squamous cells manifest one set of properties: high nuclear-cytoplasmic ratio, nuclear hyperchromatism, dehydrogenase and phosphamidase activity. These diminish and a different set of properties is found in "maturing" cells: low nuclear-cytoplasmic ratio, low nuclear chromatin, disulfide groups, and glycogen. The transition from "growth" properties to "maturation" properties is gradual. No sharp demarcation in them occurs as cells pass from normal portio vaginalis mucosa to metaplasia to dysplasia to intraepithelial carcinoma to invasive squamous-cell carcinoma of the cervix.

After seven years of intensive study with so little concrete result, one must take pause. Necessarily we have some of the same feeling that must have come to Jacob when he lifted the bridal veil and discovered Leah rather than Rachel. The studies have been intrinsically fascinating to us in detail. We hope that we have made some slight contribution to the general body of knowledge concerning cervical carcinoma. Certainly one cannot become discouraged as long as the basic problems of carcinoma of the cervix remain to be solved. There must be some sharply differentiating feature in structural detail, chemical composition, or biophysical characteristic between malignant and nonmalignant cervical squamous epithelial cells. When such a differentiating characteristic is found, the diagnosis of early cervical carcinoma will be much more accurate, the treatment more efficacious. Many new methods of

cell study are developed each year. Our current endeavors include review of the squamous epithelium of the cervix with the interference-contrast microscope, a new research tool of considerable potential.[2]

Summary

As part of a continuing study of squamous cells of the uterine cervix, tissue from 72 examples of invasive squamous-cell carcinoma were subjected to a battery of histochemical techniques, including localization of dehydrogenase, alkaline phosphatase, phosphamidase, protein-bound sulfhydryl and disulfide groups, glycogen, and lipid. Comparisons were made with 68 other cervical biopsies. In general, squamous-cell carcinoma showed a reaction pattern similar to that of the basal layer of portio vaginalis mucosa, including evidence of dehydrogenase and phosphamidase activity. Keratinizing squamous cells from neoplastic and nonneoplastic epithelium contained disulfide groups. Squamous cells in superficial layers of squamous mucosa and well-differentiated squamous carcinoma cells in some cases contained glycogen. No histochemical reaction pattern peculiar to carcinoma was found. These findings are consistent with previous histochemical and physical measurement studies, in which growing squamous cells had essentially similar properties, whether they came from carcinoma or from regions of nonneoplastic proliferation.

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THE ROLE OF EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF CARCINOMA OF THE CERVIX UTERI

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EARLY diagnosis of malignancy is stressed today in many papers appearing in the medical publications and in the many conferences which meet to discuss the subject of cancer. Carcinoma of the cervix of the uterus should, theoretically, be easily detectable, both because of the accessibility of the cervix and because of the applicability of cytological methods in this field. The purpose of this paper is to report the results of systematic and routine use of Papanicolaou smears in the diagnosis of cervical carcinoma, to draw attention to some factors in the incidence of the disease, and to emphasize a few points which have tended to prevent its early detection.

The observations here recorded were made over a period of approximately 4½ years from statistics obtained at the Yates Memorial Clinic. The Clinic is sponsored by the Southeastern Michigan Division of the American Cancer Society, staffed by the Wayne State University College of Medicine, and operated as a "cancer detection" center.

Material and Methods

As in all "detection" centers, all examinees are presumably asymptomatic. The fallacy of this presumption is suggested by information elicited in a routine carefully taken history, and is further suspected because of some of the lesions encountered in the thorough physical examination. Although the examination is primarily for the recognition of early cancer, an effort is made to determine the presence of any disease, a written report which includes all diagnoses and all positive laboratory data in the clinic record being sent to the "patient's" family physician.

About 80 per cent of the registrants at the Clinic are women. Complete pelvic examinations are performed by gynecologists. Papanicolaou smears of vaginal secretions and of cervical scrapings are examined routinely. Cervical biopsies are performed in many of the cases with any visible lesion and, if possible, in all cases in which the smears are considered to be suspicious or positive.

The smears are classified as negative, atypical, suspicious, or positive. Negative smears are those which contain no abnormal cells. Atypical smears contain cells which exhibit abnormalities of a kind which does not suggest

that cancer is responsible for the alterations. Severe inflammatory lesions, for example, may produce such changes in cells. Suspicious cells are those which exhibit characteristics suggesting a malignant neoplasm but which are not sufficiently definite to justify classification as positive. Smears are classified as positive when there is no doubt as to the presence of malignant cells.

Analysis of Cytologic Screening Results

During the 4½ year period covered by this report, 15,832 women were examined, in 151, or 0.95 per cent, of whom a histopathologic diagnosis of carcinoma of the cervix was made, most of which were squamous-cell carcinomas. Very few adenocarcinomas were found and it is believed that for the purpose of this presentation little would be gained by giving special consideration to this small group. Therefore adenocarcinoma has been intentionally omitted from several of the figures.

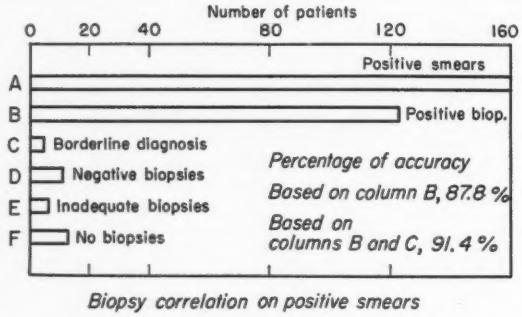

Fig. 1.—Correlation of biopsy results with positive smears.

In this group of almost 16,000 women, 160 Papanicolaou smears were reported as positive and 77 as suspicious. In 140 of the cases with positive smears biopsies were performed. Of these, 123 were reported as carcinoma, 5 were considered questionable and 7 were inadequate for satisfactory diagnosis. The term "questionable" refers to borderline or indeterminate biopsies in which atypical epithelial changes could not be accurately classified. This degree of atypism may actually represent transition from atypical hyperplasia to neoplasia; or it may be reversible, with eventual restoration to normal epithelium. It will be seen from the figures quoted that 87.8 per cent of the biopsies confirmed the positive smear diagnoses, and that 8.6 per cent were nonconfirmatory. The remaining 3.6 per cent of the smears must be regarded as so-called false positives, possibly more accurately termed "unconfirmed positives" (Fig. 1). It is usually considered that the percentages of positive smears confirmed histologically constitute the "specificity" of the test. It should be pointed out that the smear may be more correct than the biopsy, because the material in the smear may be more representative and may contain neoplastic cells from an area missed by the biopsy. The truth of this statement diminishes when a cold knife cone biopsy is performed.

In the 77 cases with suspicious smears, there were 51 biopsies, 27, or 52.9 per cent, of which were positive, and 6, or 11.8 per cent, were questionable.

One was inadequate (Fig. 2). The importance of the suspicious smear cannot be overemphasized and is well illustrated in this study.

Quite intentionally no attempt is being made in this report to document our criteria for establishing a histologic diagnosis of intraepithelial carcinoma of the cervix. We recognize the fact that opinions vary and that the problem is difficult and not free from controversy. We have been guided by conservatism and have always attempted to rule out all possibility of atypism before making a final classification of carcinoma. Care was observed that the pathologist who was responsible for the cytologic diagnoses was not the same pathologist who examined the biopsy sections; and the latter did not know the diagnosis of the smears until the histopathologic diagnosis was recorded; furthermore, many biopsies of benign lesions, from patients with cytologically negative smears, were included in the material examined. These precautions were taken to forestall any criticism of biased biopsy diagnoses, and to eliminate as far as possible the human equation.

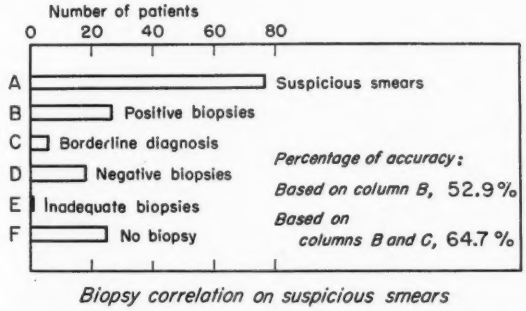

Fig. 2.—Correlation of biopsy results with suspicious smears.

Nothing has been said, up to this point, about false negative smears, that is, vaginal and cervical smears rated as free of malignant cells in cases of patients who are found, by other diagnostic methods, to have carcinoma of the cervix. The total number of such smears in this series was 7. In one case the smears were much too thick; in another the blood content was so heavy as to obscure the cells. It is interesting to note that only one of these cytologically missed cases was in the preinvasive stage; in this case the cells had been graded as atypical, so that, strictly speaking, the smear had not been considered completely negative; furthermore, the patient's return for the biopsy which proved diagnostic was solely on the basis of the atypical smear. Another biopsy performed because of a very atypical smear was diagnosed as invasive carcinoma. Nevertheless, these smears are grouped with the false negatives because definite suspicion of malignancy was not aroused by them. The fact that 6 of the false negative smears were from patients with invasive carcinoma (one was in League of Nations Stage IV, but this was the smear which was too thick for diagnostic use) is interesting. The explanation in some cases probably lies in the severe necrosis, ulceration, and bleeding which make it difficult to get fresh, well-preserved cells in the smears.

Age Incidence in Carcinoma of the Cervix

Generally speaking, cancer has been considered a disease afflicting middle-aged women and the older age group; and it has been frequently stated that cervical carcinoma is predominantly a disease of women over 40. Too strict adherence to this belief might result in failure to appreciate the substantial prevalence of cancer in younger patients. Our figures indicate that cancer of the cervix occurs with sufficient frequency in the third and fourth decades to warrant serious consideration of this aspect of the disease. Of the 151 histologically proved cases encountered at the Yates Memorial Clinic, 10, or 6.6 per cent, occurred in the third decade and 41, or 27.1 per cent, in the fourth decade (Fig. 3). One case of adenocarcinoma of the cervix was found in a woman 19 years of age. Thus 34.4 per cent, or more than one third of all cases, were found in patients below the age of 40 years, an age at which many persons believe that the hazard of cancer begins.

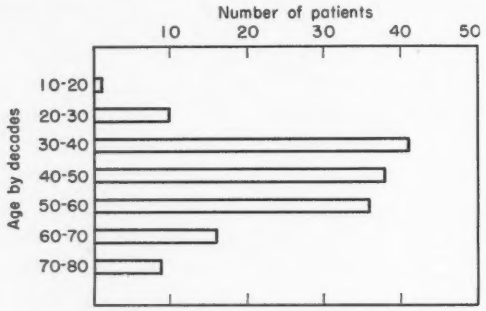

Fig. 3.—Correlation of age, by decades, with carcinoma of the cervix, all types.

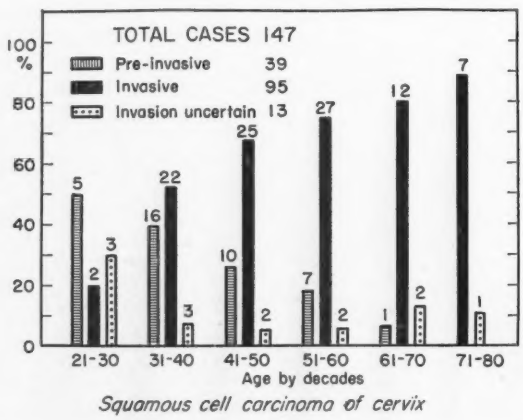

Fig. 4.—Correlation of age, by decades, with invasive status, in squamous-cell carcinoma.

It might be argued that so many cases were found in the younger patients because these were cases in early stages of the disease. Analysis of our figures has shown that this is not true (Fig. 4). Of the 52 cases which occurred before 40 years of age, 24 were definitely invasive. In 6 instances it was not possible to determine with exactitude whether invasion had begun. Thus approximately half of the cases in patients under 40 years of age had already progressed beyond the intraepithelial stage.

By way of contrast, it was found that only approximately one fifth of the cases in patients over 40 years of age were in preinvasive stages. This is considered significant because it indicates that invasive carcinoma of the cervix develops from a pre-existing intraepithelial or preinvasive carcinoma. In succeeding decades the number of intraepithelial carcinomas progressively diminishes. Between the ages of 60 and 70 there was only one such case in our series.

Correlation of Clinical State and Presence of Carcinoma of the Cervix

The value of cytodiagnosis as a screening procedure is well illustrated by the number of instances in which no clinical evidence of cancer of the cervix was present. The details of this aspect of our study are summarized in Fig. 5.

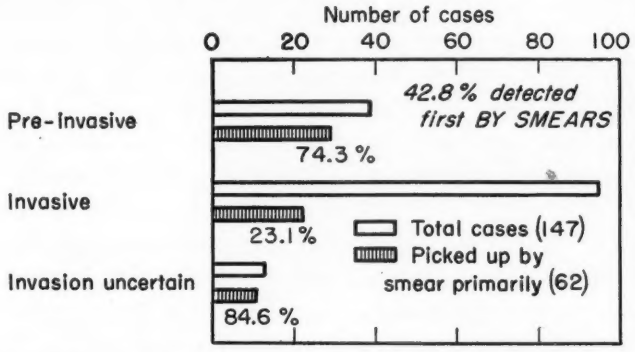

Fig. 5.—Correlation of pathologic findings with effectiveness of routine cytologic examination.

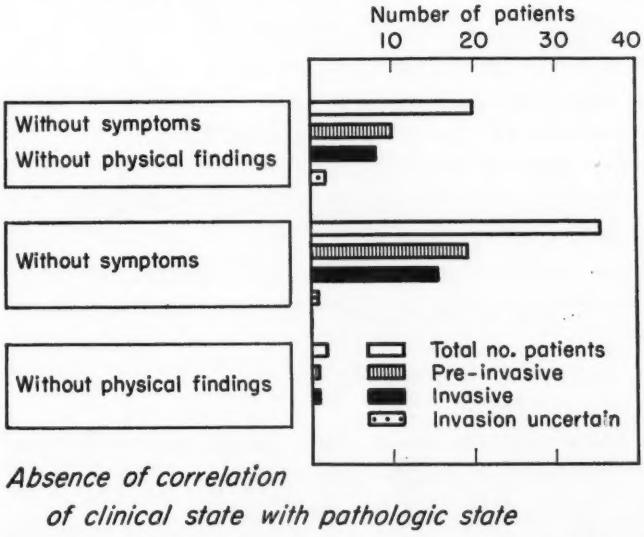

Fig. 6.—Lack of correlation between clinical and pathologic states.

Of a total of 147 cases of squamous-cell carcinoma, 63, or 42.8 per cent, were detected primarily by smear examination. Contrary to what might be assumed, these were not all preinvasive. In the figure they have been separated into three groups, the preinvasive, the invasive, and those in which the presence or absence of invasion cannot be definitely decided. As would be expected in the preinvasive group, a high proportion, approximately 75 per cent,

were first detected by smears. The most significant figure is seen in the group of frankly invasive carcinomas. Here over 23 per cent were clinically undetectable and would have been missed completely in the absence of cytologic studies.

It is impossible to emphasize too strongly how little correlation there frequently is between the clinical and the pathologic diagnosis (Fig. 6). In classifying patients for the purpose of this study, the expressions "without physical findings" and "without symptoms" were interpreted in the strictest sense of the words. The most minor details, e.g., mild cervicitis, healed laceration, slight reddening, etc., were considered sufficient to eliminate a case from the group classified as without physical findings. Only those described in such terms as "cervix looks clean," "cervix normal," etc., were included in this group. Similarly, no patients with any symptoms related to the pelvis or abdomen were included in the group without symptoms. The most interesting, and the most significant, part of this figure is the finding that 8 patients with invasive cervical cancer were free of any abnormalities which could be suspected by history or physical examination. It is well to remember that as many as 90 per cent of carcinomas of the cervix spread upward into the endocervical canal, and not out upon the portio,[1] and are, therefore, difficult or impossible to detect by physical examination alone, particularly in the early stages of the disease.

Summary and Conclusions

1. In a group of 15,832 presumably asymptomatic women from whom routine Papanicolaou smears were obtained, the incidence of histologically proved carcinoma of the cervix was 0.95 per cent.

2. Biopsies were positive in 87.8 per cent of cases with positive Papanicolaou smears; in 52.9 per cent of those with suspicious smears.

3. Of the 147 cases of histologically proved squamous-cell carcinoma of the cervix, 95 were invasive, 39 were apparently preinvasive. The status of the remainder was uncertain.

4. Nearly one fourth of the invasive and approximately three fourths of the preinvasive carcinomas of the cervix were not recognized on vaginal inspection; therefore

5. History and physical examination *only* are not reliable methods for the diagnosis of cervical carcinoma.

6. Routine Papanicolaou smears have been a most effective diagnostic aid in cancer detection and are credited with primary detection of 42.8 per cent of all cancers of the cervix at Yates Memorial Clinic.

7. Approximately one third of the biopsy-positive cases of cervical carcinoma in this series occurred before the age of 40 years. Almost one half of these had already reached an invasive stage. Therefore this disease is more an affliction of the younger age group than it has been generally thought to be.

Reference

1. Scott, Roger B., and Reagan, James W.: J. A. M. A. 160: 343, 1956.

FEMINIZING MESENCHYMOMAS (GRANULOSA-CELL AND THECA-CELL TUMORS) WITH ASSOCIATED ENDOMETRIAL CARCINOMA

Review of the Literature, and a Study of the Material of the Ovarian Tumor Registry

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(From the Department of Obstetrics and Gynecology, School of Medicine, University of Pennsylvania and the Ovarian Tumor Registry)

MANY writers have reported the association of a feminizing ovarian tumor and carcinoma of the endometrium. The statement has often been made that while feminizing ovarian tumors frequently occur during reproductive life, it is only when this tumor occurs just before or after the menopause that there is an increased risk of endometrial cancer.[11, 27, 28, 31]

The finding of a malignant granulosa-cell tumor associated with a carcinoma of the endometrium in a woman who was only 33 years of age at the Hospital of the University of Pennsylvania prompted a report of this case, a review of the literature, and a study of the material of the Ovarian Tumor Registry.

It is felt by several investigators that both the granulosa-cell tumor and thecoma arise from the undifferentiated cells of the ovarian mesenchyme.[15, 16, 37] In many of these tumors both granulosa and theca cells can be found. The term feminizing mesenchymoma introduced by Novak is used in this paper to refer to both of these tumors. This seems to be a more inclusive term embracing the granulosa-cell tumor, the thecoma, and those tumors in which both types of cells are present.

Review of the Literature

Schröder[46] in 1922 was the first to report the association of a granulosa-cell tumor with carcinoma of the endometrium. Ingram and Novak[27] reviewed the literature from 1920 to 1949 and reported 4 cases. A review of the literature since 1949 discloses 67 additional cases (Table I). Although detailed clinical histories were not always given, in only one instance was the association of these two tumors reported in a woman less than 40 years of age. This was a woman 34 years of age with bilateral thecomas and an associated adenoma malignum of the endometrium reported by Giordini[21] in 1949.

Ingram and Novak in their review found 28 thecomas and 22 granulosa-cell tumors associated with carcinoma of the endometrium. This was a very interesting finding in view of the fact that the thecoma is thought generally

TABLE I. CASES OF FEMINIZING MESENCHYMOMAS OF THE OVARY ASSOCIATED WITH CARCINOMA OF THE ENDOMETRIUM REPORTED IN THE LITERATURE SINCE 1949

AUTHOR	YEAR	OVARIAN TUMOR TYPE	UTERINE TUMOR	NUMBER OF CASES	COMMENT
Falls, Ragins, and Goldenberg	1949	Thecoma	Adenocarcinoma	1	Report of 39 granulosa-cell tumors
Giordini	1949	Thecoma	Adenocarcinoma	1	Case report of bilatera thecomas
Sternberg and Gaskill	1950	Thecoma	Adenocarcinoma	1	Report of 12 thecomas
Weiner	1950	Thecoma	Adenocarcinoma	1	Case report
Henriksen	1950	Granulosa Thecoma	Adenocarcinoma Adenocarcinoma	1 1	Report of 336 cases of carcinoma of the endometrium
Grey	1950	Granulosa	Adenoacanthoma	1	Case report
Randall, Mirick, and Wieben	1951	Feminizing ovarian tumor. Type not stated	Adenocarcinoma	5	Report of 330 cases of carcinoma of the endometrium
Dockerty and Mussey	1951	Granulosa Thecoma	Adenocarcinoma Adenocarcinoma	2 1	13 cases previously reported
Bredland	1951	Granulosa	Adenocarcinoma	1	Case report. Patient also has carcinoma of the breast
Corbet, Miller, and Tod	1952	Thecoma Granulosa	Adenocarcinoma Adenocarcinoma	1 1	Case report
Conill-Serra	1952	Thecoma	Adenocarcinoma	1	Case report
Hinz	1952	Thecoma	Adenocarcinoma	1	Case report. Also adenomyosis
Muller	1952	Granulosa	Adenocarcinoma	4	Case reports
Huber	1953	Granulosa Thecoma	Adenocarcinoma Adenocarcinoma	5 7	Report on feminizing ovarian tumors and carcinoma of the endometrium
Duckett, Davis, and Fetter	1953	Granulosa	Adenocarcinoma	1	Report of 17 granulosa-cell tumors
Gylling	1953	Granulosa	Adenocarcinoma	1	Report of 19 cases of granulosa and theca-cell tumors
Larsson and Olson	1954	Thecoma	Adenocarcinoma	1	Possibly bilateral
Way	1954	Feminizing ovarian tumor. Type not stated	Adenocarcinoma	5	Review of 89 cases of carcinoma of the endometrium
Lienhard and Halliburton	1954	Granulosa	Adenocarcinoma	1	Report of a case
Mayer	1955	Thecoma	Adenocarcinoma	1	Report of a case
Mansell and Hertig	1955	Granulosa Granulosa-theca-cell tumor Thecoma	Adenocarcinoma Adenocarcinoma Adenocarcinoma	1 2 8	Report of granulosa-theca-cell tumors and endometrial carcinoma
Biggart and Macafee	1955	Granulosa Thecoma	Adenocarcinoma Adenocarcinoma	3 5	Report of 18 granulosa-cell tumors and 25 thecomas
Peel	1956	Granulosa	Adenocarcinoma	2	Report of 107 cases of endometrial carcinoma

to be a rarer tumor than the granulosa-cell tumor. The point was made by them that in the first 500 cases of the Ovarian Tumor Registry, only 6 thecomas were encountered as compared to 67 granulosa-cell carcinomas.

Review of the literature since 1949 shows 24 granulosa-cell tumors, 2 granulosa-theca-cell tumors and 31 thecomas associated with carcinoma of the endometrium. In 10 instances the type of ovarian tumor was not stated, the tumor being designated as a feminizing tumor. Again, a large number of thecomas appears. A preponderance of these tumors has appeared in the more recent reports upon feminizing mesenchymomas.[2, 15, 31] The true incidence of thecomas is not yet appreciated and many such tumors may have been diagnosed as fibromas heretofore.

Satisfactory clinical histories were obtainable in only 30 of 67 cases reported since 1949. The remaining cases were merely mentioned in papers relative to this subject or were reported in inaccessible foreign medical journals.

In the 30 histories that were analyzed, there was one patient 34 years of age, as previously mentioned. Of the remaining cases the average age was 63, the youngest being 53 years and the oldest 83. Fifteen were in the seventh decade. In all instances but one, the uterine tumor was an adenocarcinoma, the one exception being an adenoacanthoma. The most common symptom in these cases was postmenopausal bleeding.

Emge[13] found no cases of carcinoma of the endometrium associated with 29 granulosa-cell tumors and 14 thecomas in the files of the Stanford Gynecological Laboratory and Department of Pathology of Children's Hospital of San Francisco. In a total of 753 feminizing ovarian tumors collected from various teaching centers by Emge, ony 25 endometrial malignancies were found. He felt strongly that there is no relation between the feminizing ovarian tumor and endometrial carcinoma, and that some other factor than estrogen was operative in producing the high incidence of endometrial cancer reported by others.

Present Study

The following is a case report of a woman 33 years of age cared for at the Hospital of the University of Pennsylvania. Material of the Ovarian Tumor Registry is then presented.

CASE 1.—History No. HUP 04 88 49. A 33-year-old gravida i, para i, was admitted to the Hospital of the University of Pennsylvania with the chief complaint of vomiting and gaseous distention of 11 days' duration. Menorrhagia had occurred during the last year, but no metrorrhagia.

Examination showed an obese, moderately ill woman who weighed 190 pounds. The abdomen was distened by ascites. Pelvic examination showed a normal cervix with blood at the os. The uterus could not be outlined. Nodulations were felt in the posterior cul-de-sac.

A dilatation and curettage obtained abundant curettings grossly resembling carcinoma. At laparotomy, the peritoneum, omentum, and bowel were studded with tumor nodules. The ovaries were replaced by large masses of fungating friable tissue. Biopsies were taken from the ovaries and omentum; further surgery was not attempted.

Pathology Report No. A-18075.—The specimen consisted of curettings and 7 fragments of tissue from the ovary and omentum.

Microscopic examination: The biopsies of the omentum and ovary were composed of tissue of quite different structure from that of the endometrium. The cells showed a microfolliculoid appearance with occasional rosettelike groupings about Call-Exner bodies, typical of granulosa-cell carcinoma.

The curettings showed endometrial glands composed of stratified cells with loss of cell polarity. In many areas, all semblance of basement membrane was lost and there was free invasion of the surrounding stroma by epithelial cells with numerous mitotic figures.

Diagnosis: Granulosa-cell carcinoma of the ovary with metastasis to peritoneum, bowel, and omentum; carcinoma of endometrium (Figs. 1 and 2).

Fig. 1.

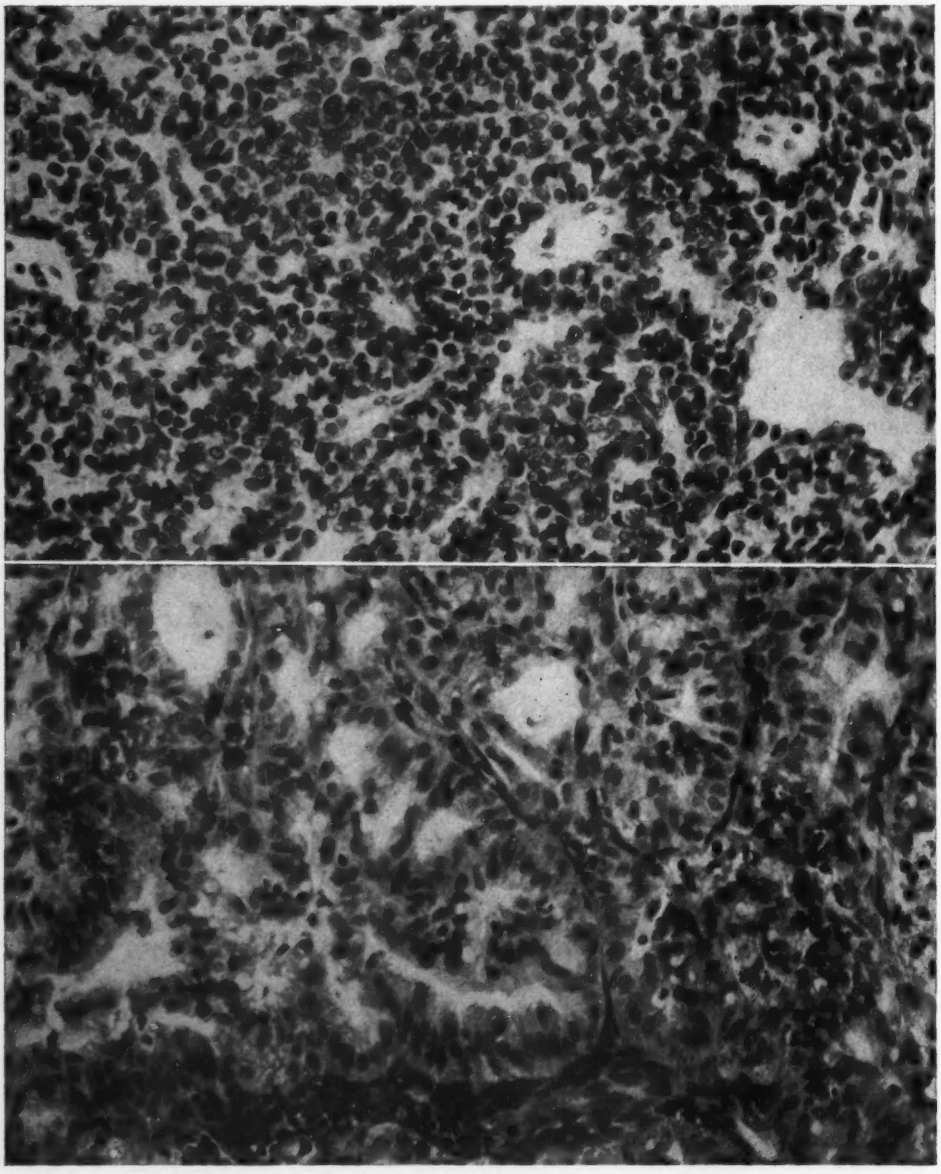

Fig. 2.

Fig. 1.—Case 1. Ovarian tumor showing granulosa cells with tendency to rosette formation.

Fig. 2.—Case 1. Uterine curettings showing adenocarcinoma of endometrium.

The ovarian Tumor Registry of the American Gynecological Society at present contains the slides and clinical histories of over 1,550 tumors. These

are reviewed by each member of the committee.* The diagnoses are reviewed by the Chairman and a final classification reached. Usually the material sent to the Registry represents a rare or difficult problem for the physician who submits the tissue. Therefore, the relative frequency of the various tumors in the Registry does not give the true incidence of these lesions as they are encountered in practice.

Two hundred and eighty-nine tumors have been classified as feminizing mesenchymomas (Table II). Busby and Anderson[4] have reported upon 107 feminizing mesenchymomas of the Ovarian Tumor Registry with a 5 year follow-up. The present study includes all those tumors in the Registry at present in which the endometrium was available for study.

TABLE II. CLASSIFICATION OF FEMINIZING MESENCHYMOMAS IN THE OVARIAN TUMOR REGISTRY

Granulosa-cell tumor	169
Granulosa-cell tumors, luteinizing	10
Granulosa-thecoma	33
Thecoma	76
Luteoma	1
Total	289

Both the ovarian tumor and the endometrium were available in 56 instances. Among these, there were 13 instances of a feminizing ovarian tumor associated with a carcinoma of the endometrium (Table III).

Study of the records discloses that all but one of the patients were in the older age group. This patient was 37 years of age, with the chief complaint of menorrhagia, who had a 12 by 12 by 10 cm. cystic granulosa-cell tumor of the left ovary associated with a carcinoma of the endometrium. Total hysterectomy and bilateral salpingo-oophorectomy were performed. The patient is reported living and well 5 years following the procedure.

Of the remaining patients the youngest was 50 and the oldest 73. In 10 of these patients the menopause occurred late, that is, at 49 to 53. One patient had an artificial induction of the menopause by irradiation at the age of 46. In one patient the time of menopause is not known. The symptom common to all these patients was postmenopausal bleeding.

In all but 3 patients, there was a relatively short delay between the onset of vaginal bleeding and definitive treatment. The one patient (OTR No. 975) in whom there was a 12 year delay between symptoms and treatment was reported by Ingram and Novak[27] to be well 6 months after operation. Further follow-up has shown, however, that the patient succumbed to widespread metastases from the endometrial carcinoma within a year of the operation. Follow-up was not obtainable in 2 cases. One patient died of heart disease 2 days following operation. Nine patients are still living from 1 to 8 years following treatment.

One patient received therapeutic irradiation and 6 years later a luteinized granulosa-cell tumor was found. This is very interesting in view of the fact that these tumors have been produced experimentally by light irradiation of mice.[18] McKay, Hertig, and Hickey[33] have reported a case of a granulosa-cell tumor in a woman 38 years of age following exposure to roentgen-ray irradiation. On the other hand, Speert[48] found a very low incidence of ovarian tumors in a group of irradiated women. Only one was found to have a granulosa-cell tumor.

In 5 of the cases, the uterine tumor showed definite invasion of the myometrium and was the cause of death in one instance. In the other cases the

*Currently the committee consists of Drs. Emil Novak, Chairman, George H. Gardner, Carl T. Javert, Arthur T. Hertig, and Robert L. Faulkner.

TABLE III. CASES OF FEMINIZING MESENCHYMOMAS WITH ASSOCIATED ENDOMETRIAL CARCINOMA IN FILES OF THE TUMOR REGISTRY

OVARIAN TUMOR REGISTRY NUMBER	AGE	PARITY	SYMPTOMS	PATHOLOGY	TREATMENT	RESULT
11	50	0	Eight weeks of vaginal bleeding. Six years previously was given abdominal x-ray and 4 years previously given intracavitary radium for menometrorhagia	Luteinized granulosa-cell tumor of left ovary 6 by 4½ by 4½ cm. Adenocarcinoma of the uterus invading myometrium. Endometrial polyps	Total hysterectomy with bilateral salpingo-oophorectomy	Lost to follow-up
186*	60	iii	Menopause at 50. Vaginal spotting for 3 months	Granulosa-cell tumor of left ovary 10 by 3 by 7 cm. Adenoacanthoma of endometrium invading myometrium. Squamous-cell metaplasia of cervix	Total hysterectomy. Left salpingo-oophorectomy. Right ovary previously removed	Has had abdominal perineal resection for carcinoma of rectum 2 years ago. Living and well now, 8 years
418	63	0	Menopause at 51. Vaginal bleeding every 3 months for 3 to 4 days for last 2 years	Thecoma of right ovary 11 by 10 by 8 cm. Uterus normal size with adenocarcinoma of endometrium	Curettage. Bilateral oophorectomy	Lost to follow-up
432*	54	ii	Menopause at 49. Vaginal spotting one week	Granulosa-cell tumor of right ovary 12 cm. in diameter. Adenocarcinoma of endometrium invading the myometrium	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 6 years
631	37	ii	Regular menses until the last year. Given estrogen which resulted in profuse periods	Granulosa-cell tumor 12 by 12 by 10 cm. Cystic mass. Uterus normal size with adenocarcinoma of endometrium	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 5 years later
776	67	iv	Menopause at 50. Vaginal bleeding for 3 years. Pain in left lower quadrant for 2 to 3 months	Curettage showed adenocarcinoma. Bilateral ovarian thecomas	Curettage. Laparotomy with biopsy of ovary	Died 2 days later with heart disease

791	66	0	Menopause date not given. Vaginal bleeding 2 days' duration	Thecoma of ovary consisting of numerous small bright yellow circumscribed areas 1 to 3 cm. in diameter. Adenocarcinoma of endometrium and postmenopausal hyperplasia	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 5 years
805	68	iv	Menopause at 50. Eight weeks of vaginal bleeding. Had bilateral mastectomy for scirrhous carcinoma of breast 3 years previously	Normal-sized ovaries, one containing a 1 cm. granulosa-theca cell tumor. Adenocarcinoma of endometrium	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 4 years later
872	69	ii	Menopause at 49. Vaginal bleeding one month	Thecoma of ovary, 2 cm. in diameter. Adenocarcinoma of endometrium	Intracavitary radium and total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 3 years later
975*	73	0	Menopause at 50. Vaginal spotting for 12 years	Thecoma of left ovary 12 cm. in diameter. Adenocarcinoma of endometrium invading the myometrium. Squamous metaplasia of cervix	Intracavitary radium and total hysterectomy. Bilateral salpingo-oophorectomy	Died after one year of metastatic endometrial carcinoma
1016†	64	0	Menopause at 50. Vaginal spotting and discharge for 8 months	Thecoma of right ovary, firm yellow tissue 1.5 by 2 by 2 cm. in diameter, tumor circumscribed and yellow. Possible thecoma left ovary	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 3 years later
1090	70	0	Menopause at 53. Vaginal spotting and discharge for 4 months	Thecoma of right ovary 1 cm. in diameter. Brenner tumor of left ovary. Adenocarcinoma of endometrium with invasion	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well 3 years later
1131	60	0	Menopause at 50. Vaginal bleeding for two months. No adnexal mass	Thecoma of right ovary, size of hazelnut. Adenocarcinoma of endometrium	Total hysterectomy. Bilateral salpingo-oophorectomy	Living and well one year

*Cases 186, 432, and 975 were reported by Ingram and Novak[37] in 1951.
†Reported by Larsson and Olson[39] in 1954.

Fig. 3.

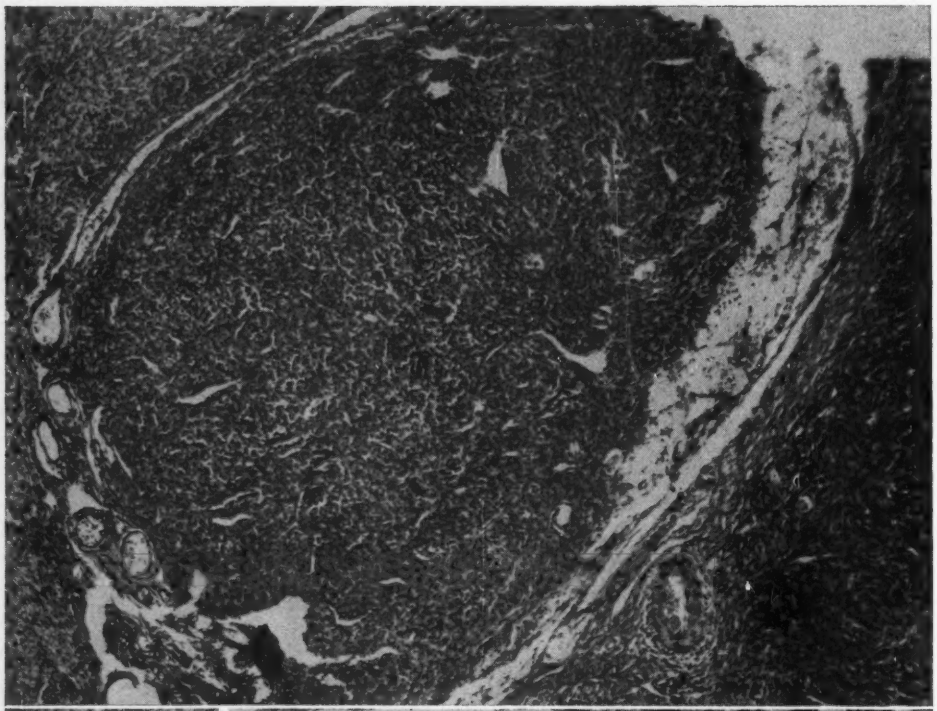

Fig. 4.

Fig. 3.—Case 2. Ovary, low power showing small granulosa-theca-cell tumor.
Fig. 4.—Case 2. Uterus, showing adenocarcinoma of endometrium invading uterine wall.

carcinoma was still confined to the endometrium. The ovarian tumor in 8 cases was a thecoma and in 5 a granulosa-cell tumor, which tends to support the finding that the thecoma is more frequently encountered than the granulosa-cell tumor when there is an associated carcinoma or hyperplasia of the endometrium.

The ovarian tumors were not exceedingly large, the largest being 12 cm. in diameter. In 6 cases the tumors were found in a grossly normal ovary when it was bisected. Therefore, in 7 cases a definite adnexal mass could be palpated on pelvic examination and in 6 cases no enlargement of the ovary was detectable by pelvic examination.

This is again illustrated by a case of a feminizing mesenchymoma associated with a carcinoma of the endometrium recently submitted to the Ovarian Tumor Registry, reviewed by the Chairman, Dr. Novak, but not yet circulated to the other members of the committee. A brief report is included with photomicrographs. The ovary contained a small tumor less than 1 cm. in diameter which was not discernible by bimanual pelvic examination.

CASE 2.*—A 66-year-old white woman, gravida vi, para iv, with 2 abortions, consulted her physician because of one episode of vaginal bleeding 3 weeks previously. Since then, she had had a heavy leukorrhea. Her menses had ended with a normal menopause at age 53.

Pelvic examination showed a greenish-yellow discharge coming from a small cervical os. The uterus was 1½ times normal size. No adnexal masses were palpable.

A dilatation and curettage showed an adenocarcinoma.

A total hysterectomy and bilateral salpingo-oophorectomy were then performed. The ovaries were not enlarged but, on bisection, a small, firm, yellow mass less than 1 cm. in diameter was found in one. The endometrial cavity contained a friable, hemorrhagic tumor.

Microscopic Examination.—Section of one ovary showed areas of stromal hyperplasia. There was a circumscribed mass of tumor contained within the ovary. Some of the cells appeared to be epithelial and there was a tendency to form clusters and rosettes.

The other ovary showed stromal hyperplasia.

Sections of the uterus showed adenocarcinoma invading the myometrium.

Diagnosis.—Granulosa-theca-cell tumor of ovary; stromal hyperplasia of ovary (bilateral); adenocarcinoma of the endometrium (Figs. 3 and 4).

The difficulty in distinguishing adenocarcinoma from atypical hyperplasia of the endometrium was emphasized by Schröder[46] and Meyer[34] in the original report of the first case of concurrent granulosa-cell tumor and carcinoma of the endometrium. Other authors have since re-emphasized this difficulty.[38, 39]

Over a 20 year period at the Hospital of the University of Pennsylvania, 17 feminizing mesenchymomas have been encountered in which the endometrium was also available. In these cases the endometrium showed carcinoma in 1, atypical hyperplasia in 1, endometrial hyperplaisa in 7, retrogressed hyperplasia in 2, proliferative phase in 4, and atrophy in 2. The case of atypical hyperplasia was difficult to distinguish from adenocarcinoma. The case represented a malignant granulosa-cell tumor with a markedly atypical endometrial hyperplasia.

Comment

The simultaneous occurrence of a feminizing mesenchymoma and carcinoma of the endometrium is thought provoking because of the possible carcinogenic properties of estrogens. Schuschania,[47] demonstrating an increased

*Courtesy of Drs. Emanuel Fliegelman and William Silverman, Philadelphia, Pa.

amount of urinary estrogen and estrogen in tumor tissue, was the first to show that the granulosa-cell tumor produces this hormone. Subsequent reports have confirmed this fact.[41] Whether this hormone can incite the development of endometrial cancer is a moot question. It has been shown experimentally that estrogen can produce endometrial hyperplasia and that a markedly atypical hyperplasia can be produced by estrogen administration in the laboratory animal and the human.[7, 14, 36, 44] While carcinoma has been observed in women receiving estrogen, it cannot be said at present that estrogens are carcinogenic.[17, 20, 40, 51]

It is indeed interesting that 10 to 27 per cent of feminizing mesenchymomas are associated with endometrial cancer.[1, 9-11, 27, 31] In many other instances of feminizing mesenchymomas, such an atypical endometrial picture is seen that they are practically indistinguishable from carcinoma. Perhaps we are observing a "spontaneous biologic experiment in the human being."[50]

Summary

1. A case of granulosa-cell tumor associated with a carcinoma of the endometrium in a woman 33 years of age is reported. This association has not been reported previously in a woman under 40 in the English literature. There is one case reported in the South American literature by Giordini of a woman 34 years of age with bilateral thecomas and carcinoma of the endometrium.

2. A review of the literature since 1949 on feminizing mesenchymomas associated with endometrial carcinoma is presented.

3. The feminizing mesenchymomas of the Ovarian Tumor Registry in which the endometrium is available were reviewed. Those with associated endometrial cancer are reported. There was only one case in a woman in the reproductive age.

4. This report now brings the total number of instances of these combined tumors to 132, of which 3 were in women under 40.

I wish to express my appreciation for access to the Ovarian Tumor Registry of the American Gynecological Society permitted by the late Dr. Emil Novak, and for his invaluable aid in the preparation of this manuscript. I am also indebted to Dr. Horatio T. Enterline and Dr. Douglas P. Murphy for their constructive criticisms and helpful suggestions.

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IDENTIFICATION OF AND THERAPY FOR VAGINAL CANDIDIASIS

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VAGINAL fungus infection problems continue to constitute a major portion of the gynecologist's practice, be it clinic or private. *Candida albicans* is the fungus that is most often implicated. Reports are now appearing that indicate other species of Candida will produce human pathology.[1, 2]

The mechanism whereby Candida become pathogenic is not known. They may be present in the vaginal canal without symptoms. Since the advent of the broad-spectrum antibiotics, the importance of fungus infections has increased.[3-6]

To the well-trained clinician, the diagnosis of moniliasis is not too difficult in frank cases. The microscopic identification of Monilia is easy for the well-trained eye. However, many presenting complaints and physical findings do not point conclusively to a correct clinical diagnosis. For such cases culture diagnosis is imperative for proper medical management. The host of therapeutics available for treatment of moniliasis is familiar to all.

We would like to report on our experiences in the culture diagnosis of all suspected cases of candidiasis (moniliasis) and review the treatment in proved cases at the Walter Reed Out-patient Gynecology Department. Attempts were made to follow all treated patients with cultures to determine the effectiveness of the therapy.

History

Fungus infections of the vagina have been reported for over a century. The first successful inoculation of Candida (Monilia) in a woman's vaginal tract was reported by Haussmann[7] in 1875. Hesseltine, Borts, and Plass[8] have confirmed these earlier experiments.

Diabetes mellitus and pregnancy are known to favor the growth of vaginal fungi.

On review of the literature, the incidence of candidiasis (moniliasis) has been reported from a low of 0.74 per cent to a high of 66.7 per cent. These reports have included the symptomatic and asymptomatic cases, obstetrical as well as gynecological cases (Table I).[9-18]

Material

Our clinical cases were mainly in the wives of service personnel stationed in and around Washington, D. C. Of the 23 obstetrical patients, 17

were white and 6 were Negro, 73 per cent and 27 per cent, respectively. There were 35 white and 15 Negro gynecological patients, a distribution of 70 per cent and 30 per cent, respectively.

All of these patients had presenting complaints referable to the lower generative tract, i.e., malodorous vaginal discharge of varying amounts, itching, burning, and general discomfort, particularly on walking. In other words, symptoms of a vaginal infestation were present. Following a history, each patient was given a careful examination. In any clinically suspected case of candidiasis a culture was made.

TABLE I. REPORTED INCIDENCE OF VAGINAL CANDIDIASIS

INVESTIGATOR	TYPE OF PATIENT	NO. OF CASES	DIAGNOSIS	INCIDENCE NO.	INCIDENCE %	SYMPTOMS PRESENT
Von Herff[9]	Obstetrical	2,010	--	15	0.74	Yes
	Gynecological	11,273	--	9	0.08	Yes
Plass, Hesseltine, and Borts[19]	Obstetrical	18	Culture	12	66.70	Yes
	Gynecological	45	Culture	11	24.40	Yes
	Obstetrical	46	Culture	15	32.60	No
	Gynecological	39	Culture	6	15.40	No
Carter, Jones, Ross, and Thomas[10]	Obstetrical	200	Culture	66	33.00	No
Johnson and Mayne[11]	Obstetrical	667	Culture	247	37.00	Combined
		82		51	62.00	Yes
		82		31	33.70	No
Plass, Borts, and Hesseltine[20]	Obstetrical	48	Culture	27	56.00	Yes
		184	Culture	60	32.00	No
	Gynecological	118	Culture	21	18.00	Yes
		202	Culture	14	7.00	No
Woodruff and Hesseltine[12]	Obstetrical	100	Culture	17	17.00	Yes
			Culture	24	24.00	No
		100	Culture	25	25.00	Yes
				25	25.00	No
		152	Culture	8	5.26	Yes
				14	9.21	No
Bromberg, Brzezinski, and Raubitschek[13]	Gynecological	115	Culture	5	4.30	No
		229	Culture	24	8.00	Yes
	Obstetrical	79	Culture	8	10.00	No
		40	Culture	13	34.00	Yes
Reich et al.[14]	Gynecological	877	Culture	121	13.80	Combined
Rauramo[15]	Obstetrical	76	Culture	47	62.00	Yes
			Culture	29	38.00	No
Gardner[16]	Obstetrical	585	Culture	67	11.50	Combined
	Gynecological	419	Culture	12	2.85	Combined
Campbell and Parrott[17]	Obstetrical	836	Culture	138	15.90	Combined
	Gynecological	133	Culture	51	38.30	Yes
			Culture	82	61.70	No

Diagnosis

With a sterile, cotton-tipped applicator a specimen was removed from the posterior fornix or lesions along the vaginal wall. The specimen was applied to the surface of a tube of Nickerson's medium.* The Nickerson's medium was contained in a small, screw-capped vial. After seeding the culture

*The Nickerson's medium and Gentersal Cream (gentian violet cream) used in this study were supplied by the Ortho Pharmaceutical Corporation, Raritan, N. J.

the cap was loosely applied, and the patient's name and number were recorded on the vial. The culture tube was allowed to incubate at room temperature for 48 hours and was then read. A positive culture contained growth of discrete dark-brown to jet-black colonies. If no growth appeared, the patient's specimen was considered negative for Candida, and other causes for her symptoms were sought.

In a few instances we cultured the specimens on Sabouraud's medium. These invariably were reported as negative while those on Nickerson's were positive. This can, no doubt, be explained on the basis that Nickerson's medium is specific for members of the Candida species and will not support the growth of bacteria. Since bacteria will grow on Sabouraud's, they may overgrow the Candida and give false negatives as we have observed on isolated occasions when checking both media with the same specimen.

Procedure

Since the purpose of this investigation was twofold, following a positive culture diagnosis, each patient was treated for candidiasis. For this purpose a new gentian violet cream* for intravaginal use was prescribed. Each patient was given a tube of gentian violet cream that contained 15 disposable applicators. She was instructed in the simple filling technique for each applicator and told to insert one applicatorful of the cream intravaginally at bedtime until the contents of the tube were exhausted. For the average patient this afforded a 2 weeks' course of therapy. If the menstrual period occurred during therapy, patients were told to continue the daily applications during the menses. They were also instructed to avoid douching during therapy. Some patients did douche, however, and the effects are described below.

Two weeks following the cessation of therapy each patient was instructed to return to the clinic for a posttherapy culture. At this visit another specimen was taken from the posterior fornix and cultured on Nickerson's medium. If the culture was negative of Candida, the patient was considered cured and discharged. If the culture was positive, another course of gentian violet cream was prescribed. This procedure was continued until a maximum of 4 courses of therapy had been prescribed.

Results

In Table II are summarized our findings on the culture of suspected cases of candidiasis in 23 obstetrical and 50 gynecological patients. There were 19 positive cultures in the 23 obstetrical cases, which confirmed our clinical impression in 82.6 per cent of the patients. Of the 50 gynecological patients, 35 had a positive culture, confirming our clinical impression in 70 per cent of the cases.

TABLE II. INCIDENCE OF CANDIDA

TYPE	NO. CASES	NO. WITH POSITIVE CULTURE	% INCIDENCE
Obstetrical	23	19	82.6
Gynecological	50	35	70.0
Uncomplicated	42		
Postpartum	5		
Diabetic	1		
Abortion	1		
Gonococcal	1		

In any clinical evaluation of this type, patients are lost from the series for well-known reasons. Thus the effectivenes of therapy can be judged only from those cases in which follow-up studies have been obtained. Therefore,

the number of cases examined and tabulated for incidence always exceeds the number returning for follow-up. From Table III it will be noted we lost only 6 obstetrical cases and 2 gynecological patients. A maximum of two courses of therapy were used in the obstetrical cases, giving us almost complete culture cure in those followed. Similarly, the over-all culture cure in the gynecological cases was practically ideal. In 3 of the 35 cases, however, 2 courses of therapy were required, 4 required 3 courses of therapy, one required 4 courses, and one patient, after 5 courses of therapy remained culture positive. This latter case was considered a failure in spite of symptomatic improvement.

TABLE III. COURSES OF TREATMENT REQUIRED FOR CULTURE-POSITIVE CASES

COURSES OF Rx	TYPE OF PATIENT	NO. PATIENTS	NO. FOLLOW-UP	% CULTURE NEGATIVE (OVER-ALL)	% CULTURE NEGATIVE (CORRECTED)
1	Obstetrical	10	6	52.6	76.9
1	Gynecological	22	2	63.0	66.6
2	Obstetrical	3	0	68.4	99.0
2	Gynecological	6	0	80.0	85.0
3	Gynecological	4	0	85.7	97.0
4	Gynecological	1	0	88.7	99.0
More than 4	Gynecological	1	0	88.7	99.0

Many authorities have considered that fatty acid gels, jellies, or creams were equally effective in the treatment of candidiasis. We have used these preparations in this clinic but never had a real follow-up to support our impressions. In one case that was culture positive on the initial visit we used propionic acid jelly for a period of 6 months. After each course of therapy the culture for Candida remained positive. In 5 other cases after 2 courses of proprionic acid jelly, the patients were placed on gentian violet cream. All became culture-negative after one course of therapy. Although few in number, these cases illustrated to us that the mere symptomatic improvement is only a part of the true clinical picture.

Reference was made previously to the use of a douche with anti-Monilia therapy. This was a common practice. A douche was prescribed in 3 cases as well as the gentian violet cream. Following one course of therapy, all remained culture positive. When the douche was eliminated from the therapy regime, all 3 cases became culture negative following the second course. This was evidence enough to caution the patient about douching during therapy since best results were obtained without it.

TABLE IV. ASSOCIATED PATHOLOGY IN EXAMINED CASES

TYPE	NO. CASES	MONILIA POSITIVE	MONILIA NEGATIVE	TRICHOMAS POSITIVE	NON-SPECIFIC	ATROPHIC	CERVICAL EROSION	GONOCOCCAL	UNKNOWN CAUSE
Obstetrical	23	19		3	1	0	0	0	0
			4	3	0	0	0	0	1
Gynecological	50	35		6	0	1	1	0	0
			15	7	1		0	1	6

In 4 of the obstetrical cases following the eradication of the Candida, clinical symptoms of a vaginal infestation persisted. Further analysis of their discharges indicated 3 were positive for *Trichomonas vaginalis* and 1 contained nonspecific or mixed bacteria. In 3 of 4 obstetrical patients that had clinical symptoms of candidiasis but were culture negative, *Trichomonas vaginalis* was found.

Of the culture-positive gynecological patients, 6 had *Trichomonas vaginalis,* one had atrophic vaginitis, and one had a cervical erosion. For the culture-negative patients, 7 had *Trichomonas vaginalis,* one had nonspecific vaginitis, and one was positive for Gonococcus.

There were one obstetrical and 6 gynecological patients for whose symptoms no intravaginal cause could be ascertained (Table IV).

Since gentian violet imparts a color to everything that it touches, a note on the color-producing qualities of this cream is justified. The cream we used was purple in color. It stained the vaginal tissues and will stain undergarments and linen. The cream is so formulated, however, as to permit its easy removal from fabrics. The cream base, by nature of its physical characteristics, does adhere to the vaginal mucosa and is less "runny" than other gentian violet preparations. If stains do occur, patients have found them easy to remove by washing in lukewarm water with any standard alkaline soap. Detergent soaps are ineffective in removing the color. Although this has been a complaint with some of our patients, the correction of their vaginal pathology far outweighed this minor, short-term inconvenience.

In a previous study by Guttmacher[18] a preliminary clinical report was made on this cream. Although we were more selective in our clinical material, our results more than confirm his findings.

Conclusions

1. A simple, specific culture tool for candidiasis has been described.

2. Our clinical diagnosis of candidiasis based on symptomatology and physical findings is not perfect, and cultures should be used to support our impressions.

3. A gentian violet cream has been shown to be an ideal medical therapeutic agent for proved cases of candidiasis.

4. The significance of associated vaginal infestations is reported.

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STAPHYLOCOCCAL AND SUBSEQUENT CANDIDA ALBICANS ENTEROCOLITIS COMPLICATING NOVOBIOCIN THERAPY

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THERE is an abundance of material in the literature related to the problem of enterocolitis, but a paucity of information on this subject is to be found in the obstetrical and gynecological journals. The one exception, found in a brief review of the current gynecological literature, is an excellent article by Wall and Kelsey.[10] These authors reported a case of severe staphylococcal enterocolitis following hysterectomy and subsequent to therapy with penicillin, streptomycin, and tetracycline. Recovery was complete after therapy with erythromycin, chloramphenicol, and measures to combat the associated circulatory collapse. It is partially to add to the scant information on this subject in the obstetrical and gynecological literature that the following paper is presented. Another purpose is to call attention to the first case of which the author is aware, where the use of the new antibiotic, novobiocin, has been complicated by staphylococcal, then monilial, enterocolitis.

Novobiocin has only recently been released to the medical profession after announcement of its discovery was made at the Third Annual Antibiotic Symposium in Washington, D. C., in November, 1955. Many subsequent studies have borne out the evidence that this agent is highly specific in its antagonism to most strains of staphylococci, as well as to some strains of *Proteus vulgaris.*[8] The same authors noted rapid development of resistance to the drug. Various side-effects found after use of this drug have included transient leukopenia, allergic dermatitis, elevated icteric index, and the intestinal symptoms of cramps, nausea, and diarrhea. Martin and associates[6] state it does not appear likely that the use of novobiocin will be complicated by micrococcal enterocolitis because of the drug's inability to eradicate *Escherichia coli, Aerobacter aerogenes,* and *Pseudomonas aeruginosa.* They further used novobiocin as the specific treatment of micrococcal enterocolitis in 5 cases, with complete success. Mullins and Wilson,[7] after treating 30 cases of pyoderma with novobiocin, stated that no concomitant or complicated candidiasis was observed. There have been no other reports of this latter problem found to date in the literature.

Enterocolitis has been recorded following treatment with nearly all the broad-spectrum antibiotics and including the sulfonamide drugs. The organisms involved are commonly the *Staphylococcus aureus, Proteus vulgaris,* and *Candida albicans.*[2] Beta hemolytic *Staphylococcus albus,*[5] and *Pseudomonas*

aeruginosa[3] have also been reported. The disease is commonly ushered in a few days after the beginning of therapy with antibiotics, sometimes in minimal doses. Abdominal pains of a crampy nature, nausea, vomiting, and copious watery diarrhea occur and proceed to shock and circulatory collapse in severe cases. The latter, circulatory collapse, probably accounts in measure for any associated oliguria. The mortality rate may run over 20 per cent as found by Speare[9] in staphylococcal enterocolitis, while less is known regarding the incidence of death from monilial or Proteus forms of the disease. Kleckner, Bargen, and Baggenstoss,[4] noted that the disease can occur following antibiotic therapy not associated with previous surgery. Dearing and Heilman[1] have suggested that the staphylococcal enterotoxic reaction may be a different entity from pseudomembranous enterocolitis, since staphylococci have not always been found in these cases.

It is with these thoughts in mind that we present the following case, which seems to emphasize the paradoxical situation wherein novobiocin, previously reported as being most active against staphylococci, apparently resulted in the development of staphylococcal enterocolitis in this patient. In addition, as the staphylococci were eradicated, candidiasis supervened to continue the enterocolitis, another situation which has not been reported previously. Finally, while reports indicate that normal intestinal inhabitants are not susceptible to this drug, they were in this case eradicated from the intestine, although possibly with the aid of other medication.

Case Report

Mrs. S. C., a 50-year-old para iii-0-i-ii, had noted severe urinary incontinence since a difficult delivery in 1928. Previous repair by the vaginal route was done in 1937 without success. In 1948 a subtotal hysterectomy for removal of a 7 pound tumor was done. Recurrent attacks of bronchitis associated with severe cough had made her urinary condition intolerable for the past two years. Physical examination was not remarkable except for a recurrent, second-degree cystourethrocele and marked shortening of the urethra due to scarring from the previous surgery.

Laboratory examination showed the red blood count to be 3.6 million; hemoglobin 11 Gm.; white blood count 4,200; polymorphonuclear leukocytes 46 with no stab forms, lymphocytes 50, eosinophils 2, and basophils 1. The Kline test was negative. A catheterized urine specimen showed specific gravity 1.032, pH 4.5, negative to albumin, sugar, and microscopic examination. The chest x-ray was negative.

The patient was admitted to the hospital on July 6, 1956, for a Ball modification of the Marshall-Marchetti-Krantz operation. Operation was performed on July 7, 1956, under spinal anesthesia, but because of the development of a cardiac irregularity only a thorough anterior vaginal plastic procedure was done and the abdominal procedure was abandoned.

Postoperatively, novobiocin (Albamycin) was begun in oral doses of 250 mg. every 6 hours. A postspinal headache responded nicely to intramuscular caffeine sodium benzoate, after failure of analgesics, opiates, and Methergine. The postoperative temperature, pulse rate, and respiratory rate never exceeded 100° F., 100, and 16, respectively. No evidence of shock, oliguria, or serious electrolytic imbalance occurred. On July 8, 1956, however, she developed severe abdominal cramps with diarrhea, progressing overnight to profuse, watery bowel movements occurring every 15 to 30 minutes. Four doses of neomycin and

Kaopectate, one ounce every 2 hours, failed to bring any relief, so on July 9, 1956, Cremosuxidine was begun in ½ ounce doses hourly. Since there was only slight response to this latter medication, a stool smear was ordered and was reported, on July 10, 1956, "loaded with staphylococci, many red blood cells and a few white blood cells." Novobiocin was immediately discontinued and erythromycin (Ilotycin) was given in one 100 mg. dose intramuscularly, followed by 250 mg. orally every 4 hours thereafter. Only 2½ hours after the erythromycin was begun, a stool culture was taken, later revealing only hemolytic *Staphylococcus aureus* and *Candida albicans*. The erythromycin was continued for 24 hours, during which time the stools became pasty in consistency and bowel movements occurred every 3 to 4 hours. At the end of this time, July 11, 1956, a stool smear showed only many *Candida albicans* and no staphylococci, so the erythromycin was discontinued on the basis of the possibility that the Candida infection might be subsequent to this medication. Mycostatin was then begun orally in 500,000 unit doses every 4 hours, by ointment to the perineum and vulva three times a day, and by vaginal suppository twice a day, in an attempt to cure the monilial infection and to prevent its spread to the operative area. Supportive therapy with 1 Cebetinic tablet three times a day and potassium gluconate in 5 grain doses three times a day was also given orally. On this same date, July 11, 1956, the catheterized urine specimen and complete blood count were reported within normal limits. All these medicines were well tolerated orally and satisfactory fluid balance was maintained by the same route since no nausea occurred. All liquids and food were also well tolerated. On July 12, 1956, the indwelling catheter was removed and voiding occurred thereafter without excessive difficulty. On July 14, 1956, stool culture was noted to contain evidence of normal intestinal inhabitants, fewer Monilia and still no staphylococci. Only four stools occurred during that day and none during that night. Consequently, on July 15, 1956, the ninth postoperative day, the patient was dismissed to her home on Mycostatin, 500,000 units orally three times a day, and with normal bladder control.

On July 18, 1956, the stool smear showed normal intestinal flora. The patient had perfect control of her bladder function and normal bowel movements. At the time of the present writing she has continued to maintain these good results and on examination the repaired area is well supported, although a few granulations are being treated with silver nitrate. She is now approximately 6 weeks postoperative.

Comment

This disease should be considered as a distinct entity, quite consistent in its diagnostic aspects, but varying in severity. Any patient who develops evidence of intestinal cramping and loose to watery stools during or shortly after receiving antibiotic therapy should be suspected of this disorder. When stool examination then shows the disappearance of the normal intestinal flora, and abnormal intestinal organisms are demonstrated to have replaced this normal flora, the diagnosis is sufficiently established. That "sterile" stools are occasionally found is not denied, but this should not be allowed to deter adequate treatment. High fever, shock, and oliguria are evidence of overwhelming severity, but should not be required in order to establish the diagnosis. Only the cases progressing to critical illness are usually reported, while those showing only minimal symptoms and capable of being diagnosed only by a high index of suspicion and an early stool examination are frequently missed. More frequent stool examinations in these cases would undoubtedly prevent some from developing into the "high mortality" group, if appropriate therapy were given earlier.

Did the novobiocin cause the change in the normal intestinal flora by eradicating the usual intestinal organisms? This is the one aspect of the case presented where there seems room for disagreement. True, novobiocin was being given in doses adequate to change the normal flora, but by the time the first stool specimen was reported as "loaded with staphylococci," the patient had also received neomycin and Cremosuxidine. Either or both of these agents may have aided in the eradication of the usual intestinal organisms. However, the fact remains that *prior to* the development of enterocolitis these normal intestinal organisms are usually markedly diminished. Clinically, this patient's disease was evident *prior to* administration of either neomycin or Cremosuxidine. Therefore, on clinical evidence, the novobiocin probably caused the eradication of the common intestinal group of organisms, allowing the staphylococci and then the Monilia to predominate. In addition, the clinical observation that neomycin did not aggravate the condition indicates that it had little causal effect. The fact that the Cremosuxidine seemed to benefit the patient slightly would also lead one to believe that it, too, was innocent of wrongdoing. Novobiocin must have been the primary culprit.

Was novobiocin implicated in the development of the staphylococcal phase of the enterocolitis? This seems quite evident from the fact that at the time of onset of the illness the only antibiotic being given was novobiocin. Symptoms developed over a period of only 24 hours, so either resistance of the staphylococci to novobiocin occurred quite rapidly or else an already resistant strain was present prior to the illness. No stool examination was done prior to the use of novobiocin, so the latter possibility cannot be overlooked, especially since the patient had recently arrived from Michigan, where novobiocin-resistant staphylococci may abide. But in this area the drug had been released only a few weeks prior to the patient's illness, and she was the second patient to receive the drug at the Raymondville Memorial Hospital, to the best of the author's knowledge. There seems little doubt but that the agent used caused the staphylococcal enterocolitis.

Did the monilial aspect of the disorder result from the novobiocin? Again, the answer is probably yes. It seems unlikely that 100 mg. of erythromycin intramuscularly only 2½ hours prior to stool culture would have given sufficient time to allow this monilial overgrowth and enterocolitis to occur, although, on the basis of this possibility, the erythromycin was discontinued as soon as the staphylococcal phase was controlled and Mycostatin was begun as soon as the fungus became evident. It seems most likely that the monilial enterocolitis was again secondary to novobiocin. The fact that clinical symptoms did not abate upon disappearance of the staphylococci from the stool, nor so long as Monilia were predominating, indicates that this was a true monilial enterocolitis and not just a simple "overgrowth." In the author's opinion this simple "overgrowth" associated with minimal symptomatology is but the beginning of a possibly severe enterocolitis and should be treated as such.

So here we have a drug that has been shown previously not to affect the normal intestinal flora, to be specifically antagonistic to most strains of staphylococci, and not to result in monilial overgrowth. Yet in this one case each of these "advantages" of novobiocin proved to be exactly the reverse. The only factor commonly acknowledged that held true to form was the rapid development of resistance to the drug by the *Staphylococcus aureus* causing the infection, which occurred in less than 24 hours. But for every unexpected turn of events with the novobiocin, an almost miraculous result was noted with the drugs used in treating the enterocolitis. The erythromycin cured the staphylococcal phase within 24 hours. Mycostatin brought clinical improvement within three days and clinical cure within three more. Circulatory collapse, fever, oliguria, and electrolyte imbalance never became problems because of the effectiveness of these agents.

Numerous articles are available in the literature for a thorough discussion of therapy in enterocolitis and to these the reader is referred. Consequently, only a few brief comments will be made here concerning this aspect of the disease. Prophylactically, it would be wise to "screen" patients, hospital employees, and surgeons for nasopharyngeal staphylococci, and in addition to examine stool stains and cultures preoperatively on the patient. If organisms capable of causing enterocolitis are prominent, appropriate therapy should be given prior to operation. Sterile gloves and masks are indicated for those working with postoperative patients. Isolation technique should be used if the disease is suspected or proved in any patient. Promiscuous use of antibiotics should be discouraged. Any medical or surgical patient on antibiotics who develops evidence of intestinal upset should have immediate stool examination by stain and culture, followed by the appropriate therapy. While results of sensitivity tests are awaited, erythromycin should be given for staphylococcal infections, Mycostatin for monilial infections, and novobiocin for Proteus infections. More than one drug may be indicated at times. In spite of the poor result in the case being reported, novobiocin would be indicated for erythromycin- and penicillin-resistant strains of staphylococci. Serial stool examinations are indicated, for the intestinal pattern may change to one with other pathogenic organisms just as in the present case. Treatment of shock may require whole blood, vasopressors, and intravenous cortisone. Fluid balance must in many cases be maintained by electrolyte studies and indicated therapy.

Summary and Conclusions

1. The scant number of publications in the obstetrical and gynecological literature related to enterocolitis has been noted.

2. Novobiocin, contrary to previous report, has been shown probably to have altered the normal intestinal flora; to have caused quite definitely the development of staphylococcal enterocolitis; and to have most likely caused the subsequent development of monilial enterocolitis.

3. A case is reported substantiating this last statement.

4. A plea is made for earlier recognition and treatment of the entity known as enterocolitis. Prophylaxis is emphasized.

5. The apparent high rate of mortality with enterocolitis as noted in the available literature would be materially lessened if the mild and moderate cases (usually those not reported in the literature) were to be included. A high index of suspicion and a stool examination are essential for early diagnosis.

I wish to thank Dr. E. E. Baden for his apt and pertinent criticisms, Mrs. W. F. Baden for her tireless encouragement and typing, and Mr. Ray Mullins for his technical assistance.

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Medical Arts Building

OBSERVATIONS ON PACEMAKER ACTIVITY IN THE EXCISED, NONGRAVID HUMAN UTERUS

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A VARIETY of evidence from numerous sources[1-3, 8-10, 12-14, 16] reported over the past three decades has been interpreted as indicative of "pacemaker" activity in the gravid uterus. There appears to be a general agreement that the pacemakers are situated close to the junction of the Fallopian tubes with the body of the uterus. According to this view, uterine contractions are believed to originate at these sites and spread, as a gradient, over the body of the viscus.

During electromyographic studies on human uterine strips suspended in oxygenated Locke's solution, we were impressed by the marked resistance of these tissues to prolonged anoxia. Bioelectric activity continued undiminished in such preparations for at least 6.5 hours after oxygenation had been discontinued. It appeared plausible that whole uteri removed at operation should yield essentially normal electromyograms during the brief time period (10 to 20 minutes) required to complete all necessary procedures.

Method

Entire nongravid uteri were suspended from silk ligatures in a moist chamber (as shown in Fig. 1) within 5 minutes of their removal from 11 patients. Of these uteri, 3 were normal viscera extirpated at the time of vaginal plastic operations, while 8 were removed from patients with partial prolapse, fibromyomas, or menorrhagia, where it appeared on gross inspection that the organs were nonpathologic over the greater portion of their musculature. Three of these uteri were postmenopausal, from patients 45 to 70 years of age, while the remainder were from women ranging in age from 28 years to 37 years.

Silver electrodes 6 mm. in diameter (constructed as shown in Fig. 1) were brought into contact centrally with the moist superior uterine surface and on the side, as shown in the diagram. Spontaneously generated bioelectric potentials from the uterine musculature were then recorded on an ink-writing oscillograph suitably filtered. The instrument was adjusted in a manner identical to that used over a period of several years in extensive laboratory and clinical studies on the urinary bladder and ureter.[4-6, 15]

Results

In general, 4 types of deflection were distinguished in the records: (a) biphasic potentials, which we have designated as "A" and "B" waves in con-

formity with a nomenclature adopted by one of us in describing electromyograms obtained from the urinary bladder and ureter[4-6, 15]; (b) monophasic wave forms of relatively high electromotive force and long duration (average 2.56 seconds), identified as "C" deflections; (c) numerous monophasic potentials of very low electromotive force and short duration (average 0.72 second) which we have termed "D" waves. These are shown in Fig. 2.

Tracings *1, 2, 3,* and *4* represent characteristic records from 3 different uteri in which bioelectric shifts appeared simultaneously at the upper, middle, and lower uterine segments. They illustrate the biphasic wave form mentioned above. Tracing *5,* while depicting simultaneous potential change over the uterine musculature, also demonstrates the spontaneous reversal of polarity quite commonly observed in uterine as well as in other smooth-muscle electromyograms (bladder, ureter). Record *6* illustrates simultaneous bioelectric activity at the three electrodes while recording *C* and *D* deflections. In none of the tracings from these 5 uteri was there any evidence of a time lag or "gradient" spread of an impulse from the uppermost (pacemaker) to the lower electrodes.

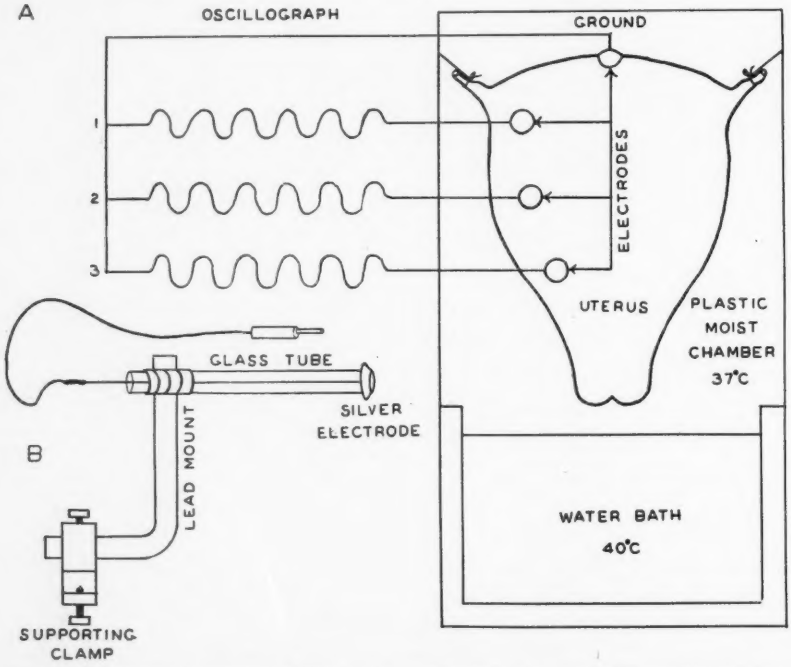

Fig. 1.—*A,* Schematic representation of apparatus for recording bioelectric potentials from the upper, middle, and lower body of the excised human uterus. *B,* Details of construction of the electrodes. Contacts were of silver, glass insulated, and were held in place on the moist uterine surface by means of flexible lead mountings.

Records *7, 8, 9,* and *10* are representative of tracings secured from 4 different uteri. They were interpreted as indicating the capacity of the upper, middle, and lower uterine segments to contract independently of each other. In other words, bioelectric activity in the lower portions of the uterus may take place without evidence of contractility in a superior segment. Record *9* was selected to illustrate the tendency of paired, biphasic potentials to occur within brief (5 to 10 second) time intervals in some uteri.

Tracing *11* might be interpreted as evidence that the musculature of the uterine cornu is dominant in its activity, were it not for recordings such as those shown in records *12* and *13.* In these uteri, activity was clearly greatest at the central and lower electrodes, respectively. In record *14,* simultaneous

potential changes under the upper and central electrodes did not spread to the lower segment of the uterus, while in tracing *15* simultaneous activity was evident under the middle and lower electrodes, while the superior musculature remained quite quiescent as regards bioelectric activity.

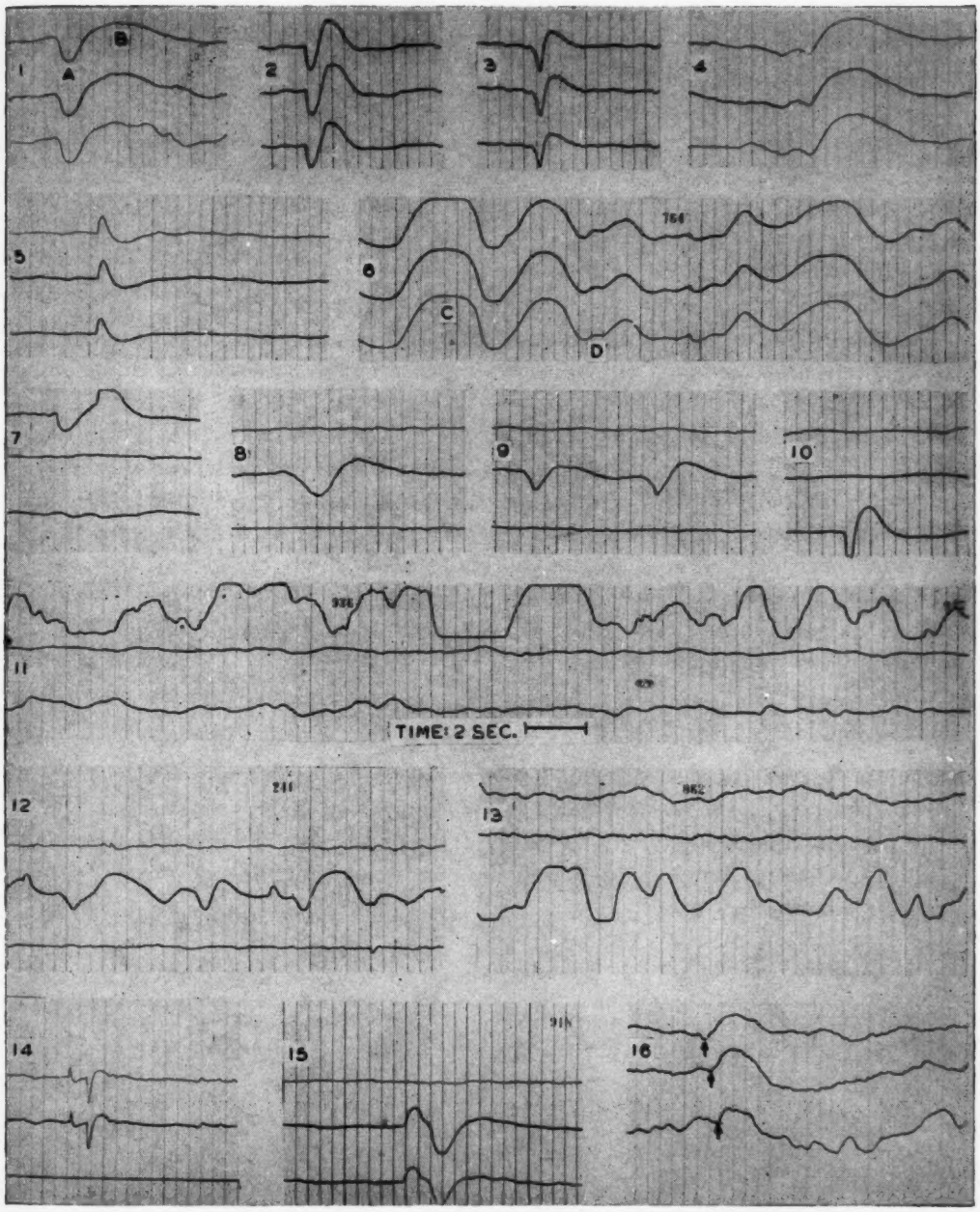

Fig. 2.—Electromyograms secured from 11 excised nongravid human uteri. Record *16* is the single instance among several hundreds of deflections examined in which the tracing gives evidence of pacemaker activity.

Record *16* was unique in our experience. In this single instance, selected from a study of many hundreds of wave complexes, a sequential time lag between the appearance of potential change at the three electrodes was rather

clearly evident. This single record could thus alone be interpreted as evidence of an activity gradient from the pacemaker, in the conventional sense, spreading over the musculature to the lower portions of the viscus.

Comment

Evidence in support of the pacemaker concept has been reported by numerous observers employing a variety of techniques: direct observation of entire gravid uteri,[9, 10, 16] intramuscular pressure changes,[1, 2, 3] and mechanograms of abdominal wall movement late in gestation and in labor, obtained by means of the tokodynamometer.[12, 13, 14] Recently Larks[11] has presented data based on electromyograms obtained through electrodes placed on the abdominal wall and "more remote points" of women in labor. All of these latter observations differ from our own in that they are based upon the gravid organ in situ. The difficulty of obtaining a sufficient number of intact, excised, gravid uteri has limited our study at the present time to the nongravid state.

In initiation of the present study it was considered that pacemaker activity should be demonstrable in the nongravid uterus when a sufficiently sensitive electromyographic technique is employed, unless, for reasons unknown, such activity is limited to the gravid uterus.

It is known that the pharmacologic action of drugs upon uterine muscle may be reversed in the gravid as contrasted with the nongravid organ[7] and it is perhaps conceivable that pacemaker activity may develop as a part of the anatomic and physiologic changes which occur during gestation. As regards the nongravid uterus, however, we have interpreted the electromyograms described as acceptable evidence of the absence of any pacemaker activity, as generally conceived, in that organ.

Summary

Electromyograms of smooth muscle activity were obtained from 11 excised, nongravid human uteri in a manner calculated to demonstrate "pacemaker" activity in the event of its presence.

With but a single exception, all of the records secured were interpreted as evidence for the absence of such activity in the nongravid human uterus.

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SIMPLE VESICOURETHRAL SUSPENSION*

A Survey

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APPROXIMATELY 7 years ago, the senior authors of this survey with Kermit E. Krantz[1] reported upon their initial experience with simple vesicourethral suspension for the correction of urinary incontinence. In the same report, a description of the operation was given as it was performed by V. F. Marshall the first time (June 8, 1944) specifically for the correction of female urinary stress incontinence. Now 12 years have passed since the procedure was initiated. The authors feel that it would be appropriate to survey and to appraise their personal experience and their results with the operation over this period of time.

It is not within the scope of this presentation to review the anatomy and histology of the bladder and urethra. Nor is it planned to present the theories of the physiology and the mechanics of micturition, nor even to explain fully the etiology of urinary stress incontinence. A few comments, however, should be made in passing over these points.

More recently, noteworthy reviews of the anatomy and histology of the bladder and urethra have been published by Giaccone[2] and Ullery.[3] One may conclude from these reviews that the descriptive and structural terminology of the anatomy and histology of the bladder and urethra still are not uniform and, at times, are confusing. It seems, however, that on one point the weight of evidence supports the concept that definitive external and internal sphincter muscles do not exist in the urethra. Krantz's[4] contribution to this concept is very convincing and we are in agreement with it.

The physiology of micturition is far from being completely understood. On the other hand, much has been contributed to the study of the mechanics of continence and stress incontinence. These advances have been made for the most part by roentgenologic techniques. In this field, the work of Millen and Read,[5] Muellner,[6] Ball, Douglas, and Fulkerson,[7] Jeffcoate,[8] and Hodgkinson[9] should be mentioned. Although the approaches to demonstrate the

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mechanics of continence and stress incontinence varied among these investigators, one could conclude that the explanation of the etiology of urinary stress incontinence was basically the same. This is the explanation that currently is generally accepted, namely, that urinary stress incontinence is caused by the lack of support of components of the levator ani to the neck of the bladder and adjoining urethra or the loss or inadequacy of the attachments of these vesical structures to the symphysis pubis. Furthermore, there is general agreement that the trauma of childbirth is most frequently the cause of this defect.

Clinical Data

This survey comprises a combined personal experience with 132 patients each of whom had a simple vesicourethral suspension. No case is included in which other procedures performed simultaneously might have provided urinary control. In other words, all of these operations were done primarily for the correction of urinary stress incontinence. Among the earlier cases, we are convinced that the operation was ill chosen in some instances, especially those in which the preoperative "stress" test was unfavorable or equivocal.

Age Incidence.—The youngest patient was 21 years of age; the oldest was 76. The average age for the entire group was 54 years.

Vaginal Findings.—There were 8 patients with well-supported vaginal walls and 9 patients with extensive vaginal scarring. The remainder had varying degrees of pelvic relaxation.

Previous History of Operations.—Sixty-five patients had had previous vaginal operations. Fifteen of these had had a total of 35 operations on the bladder or urethra for difficulties in urinary control. There were 6 among this group who had a urinary fistula into the vagina at some time before the vesicourethral suspension was performed.

Diagnosis.—The diagnosis of urinary stress incontinence in the female is not always easy to establish. A very searching history is paramount. Frequently there are psychosomatic and occasionally neurogenic elements which have considerable bearing on the case. Chronic inflammatory conditions of the bladder and the urethra especially must be eliminated. In the presence of cystitis or urethritis, a course of trial therapy must be administered before consideration of an operation for incontinence.

The preoperative elevation test or so-called "stress" test is considered one of the most important procedures of the diagnostic work-up. Not only does it help one to eliminate those who complain of incontinence and really do not have it, but it also enables one to obtain some index of whether the result of the operation will be favorable or not in those who do have stress incontinence. The test should be done in all cases and should be tried in the erect as well as the recumbent or lithotomy position. In this survey, the test indicated that the operation was advisable in 116 cases, unfavorable in 4 cases, and equivocal in 2 cases. There were 10 patients among the earliest ones in our study whose histories were considered incomplete in this regard.

Because urge incontinence is most frequently confused with stress incontinence, endocystoscopy should be done in every case. This procedure will rule out, in addition, the presence of an obstructive or degenerative lesion. By endocystoscopy, we found 16 patients with a moderate to severe degree of urethrotrigonitis. They received treatment for this condition before they were operated upon for incontinence.

Classification.—After the diagnosis of urinary stress incontinence was established in each case, 55 were classified as severe, 64 as moderate, and 13 as mild.

Some of the patients with mild urinary stress incontinence have benefited by nonsurgical treatment or by perineal exercises as recommended by Kegel[10] and Wharton.[11] Those with mild incontinence whom we operated upon thought the condition troublesome enough to warrant surgical correction.

Results.—Our results are classified as successes or failures. Among the failures are included those patients who showed some improvement over their preoperative level of loss of control, but who continued to have a mild to moderate degree of incontinence. It should be emphasized that none of the patients who showed no improvement after the operation have complained that the incontinence was ever worse.

TABLE I. URINARY STRESS INCONTINENCE TREATED BY SIMPLE VESICOURETHRAL SUSPENSION, JUNE, 1944, TO JUNE, 1954

Total number of cases	132
Immediate successful results	117 or 88.6%
Immediate failures	15 or 11.4%

The immediate results are shown in Table I. The operation proved to be immediately successful in 88.6 per cent of the cases. As the 15 failures are analyzed, it is thought that at least 6 of them should not have had the operation. Three of the failures were among those lost to follow-up. Four patients whose condition was improved over their preoperative level, but who are still incontinent to some degree, have refused further operative intervention. Two among the latter had had previous vaginal operations. The remaining 8 failures included a patient with extensive lymphogranuloma inguinale, one with chronic alcoholism, one with a psychiatric problem, a patient with a cord bladder unrecognized before operation, 2 patients whose bladders had been exposed to pelvic irradiation, 1 who developed stress incontinence following a Watkins interposition operation, one who, after failures with a sling operation, vesicourethral suspension, and the application of a tantalum mesh, finally had ureterointestinal anastomoses. It is now evident that the cases with the cord bladder, the irradiated bladders, chronic alcoholism, the psychiatric problem, and extensive lymphogranuloma inguinale were ill chosen. The patient who developed stress incontinence after a Watkins interposition, we feel, would have had a successful outcome had she had a hysterectomy combined with the vesicourethral suspension.

TABLE II. PRIMARY RESULTS AFTER LATE RECURRENCES

Immediate successful results	117 cases
Recurrences or secondary failures	6 cases
Primary successful results	111 cases
Current incidence of success with 9 months to 9 years follow-up	84%
(Only 4 cases lost to follow-up)	

There were 6 recurrences among the 117 cases with immediate good results. Table II shows that the over-all primary success of the operation currently reaches a level of 84 per cent. The time which elapsed between the immediate good result and the recurrence in these 6 patients was 9 months, 16 months, 18 months, 3 years (2 cases), and 4 years. From this it may be concluded that about 95 per cent of the patients who obtain a successful result immediately after a vesicourethral suspension may expect it to be permanent. It might be of value to summarize briefly the histories of these six cases.

CASE 1.—C. B. (NYH 1491) had had no previous treatment for incontinence. A vesicourethral suspension was performed on April 8, 1948, with an excellent result until a sudden recurrence in April, 1952. A second vesicourethral suspension was done on June 13, 1952. No complaint nor recurrence has occurred.

CASE 2.—A. C. (NYH 488395) was one in which incontinence had been present for 2 years. No previous operation had been performed. Total abdominal hysterectomy combined with vesicourethral suspension was done on Sept. 30, 1947, but stress incontinence recurred 16 months later. An anterior and posterior repair was carried out on Sept. 30, 1949, and there has been no incontinence or recurrence since this operation.

CASE 3.—E. B. (NYH 170508) had stress incontinence with moderate cystocele and rectocele. Anterior and posterior repair was done in 1937, and again in 1939, when there was a recurrence of symptoms. The incontinence was not corrected by either operation, and examination showed an extensively scarred vagina. A vesicourethral suspension was performed in January, 1945, with a good result. Loss of urinary control recurred, however, 3 years later. A third anterior and posterior repair done on April 12, 1949, resulted in correction of the incontinence with no further recurrence.

CASE 4.—T. L. (GUH 279499) complained of urinary incontinence and had bleeding fom a submucous myoma. Vesicourethral suspension combined with total abdominal hysterectomy was carried out in July, 1948, but there was a recurrence of the incontinence 9 months later. Vesicourethral suspension was repeated in May, 1949, and no further complaints nor incontinence has occurred since.

CASE 5.—F. W. (NYH 615935) had incontinence with pelvic relaxation. Anterior and posterior repair combined with a Baldy-Webster suspension of the uterus was carried out in 1945, but stress incontinence persisted. A vaginal hysterectomy with an anterior and posterior repair in 1951 did not result in any improvement of the incontinence. A vesicourethral suspension was performed on Feb. 28, 1952, and in spite of the fact that an enterocele developed 6 months later, the patient remained continent. The enterocele was repaired on Sept. 25, 1952. There was a recurrence of cul-de-sac hernia in December, 1952, but at this time the patient was still continent. In the fall of 1953, however, there was a return of the incontinence.

CASE 6.—M. E. (NYH 237873) had had stress incontinence of 10 years' duration. Anterior and posterior repair with plication of the vesical sphincter was done on July 28, 1947, but the incontinence was worse after the operation. A vesicourethral suspension was performed on July 7, 1948, with an excellent result until May, 1951, when the patient developed a mild recurrence of loss of urinary control. This patient did not consider the recurrence severe enough to warrant another operation.

As some of our primary and late failures are reviewed and re-evaluated, it is thought that in at least 5 instances, the preoperative "stress" test was misleading. Reference is made to those patients who had extensive vaginal fibrosis and scarring. The test was favorable in these instances. It is now obvious that, while the force exerted by the examiner preoperatively to elevate the bladder neck and the urethra was sufficient to overcome the defect caused by the severe fibrosis, the severe fibrosis prevented the elevation and fixation by the suprapubic route alone from being effective (Cases 2, 3, and 6). It is under such circumstances that Ball's[12] approach to the correction of stress incontinence is recommended. His operation combines the vaginal approach with the suprapubic one, thus enabling the operator to free the urethra and the bladder neck from below before elevating and fixing them suprapubically. It is also clear that in a few instances failures were the result of faulty technique in the initial operation (Cases 1 and 4).

Complications and Morbidity.—Up to the present time, the complications which we have encountered in our series have not been serious. A transient hematuria lasting from 12 to 24 hours was noted in about 75 per cent of the

cases. This type of hematuria does not require any specific treatment. Periosteitis pubis was found to complicate the postoperative course in 4 patients. These promptly responded to antibiotic therapy. Repeated catheterizations had to be resorted to in 4 cases. Cellulitis in the region of the incision was encountered on 2 occasions. Hematomas complicated the postoperative course in 4 cases. One of these was associated with a dehiscence of the wound. A suprapubic urinary fistula developed in a case where nonabsorbable material was used. The fistula spontaneously healed within a period of 3 weeks. One patient developed a postoperative incisional hernia which was subsequently repaired.

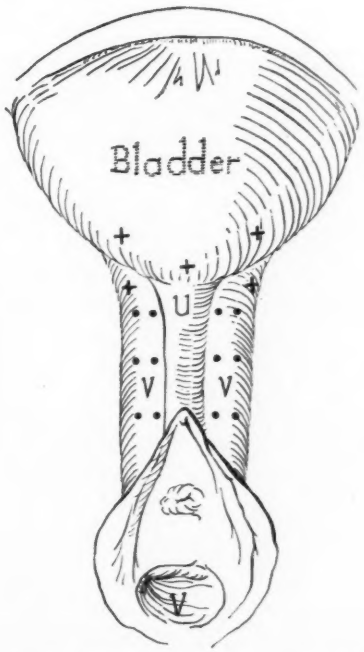

Fig. 1.—A diagrammatic sketch of the bladder, urethra (*U*), vaginal walls and introitus (*V*), showing the positions (. .) where the sutures are placed in the vaginal wall lateral to the urethra and where additional sutures (±) are placed at the junction of the urethra and bladder neck in the midline, the lateral walls of the vagina, and the musculature of the bladder.

One death occurred in this series. It was in a woman, 75 years of age, who died on the second postoperative day following a pulmonary embolism.

Pregnancy and Vesicourethral Suspension.—There were 4 women who were delivered of 5 babies after having had a vesicourethral suspension. One patient has had two spontaneous deliveries occurring 2 weeks before her expected date of confinement. The interval between the 2 pregnancies was 2 years. The first baby was born 9 months after she had had a vesicourethral suspension for severe incontinence. Incidentally, she had had a term delivery before the incontinence appeared. Two other patients had spontaneous deliveries following the operation. The fourth patient had a cesarean section close to term. The section was elected inasmuch as her previous history included not only a vesicourethral suspension for incontinence, but also a successful closure of a vesicovaginal fistula. None of these patients has reported a recurrence or loss of urinary control.

Technique.—Only a short comment need be made about the technique. The original technique of simple vesicourethral suspension has been described elsewhere and has not been altered to any great extent since then by the

authors. Two illustrations, however, are provided in this text for reference to a change which was made and described later in another communication.[13] Formerly, the lateral walls of the urethra were included by the initial sutures used to elevate and fix the urethra to the posterior surface of the symphysis pubis. This is no longer done. Fig. 1 demonstrates the position of the sutures as they are placed now. Fig. 2 shows the manner in which a suture is carried into the vaginal wall and secured to the periosteum of the pubis. A double bite into the vaginal wall is recommended instead of a single one as shown in the illustration.

The basic principle of the procedure is to keep it as uncomplicated as possible.

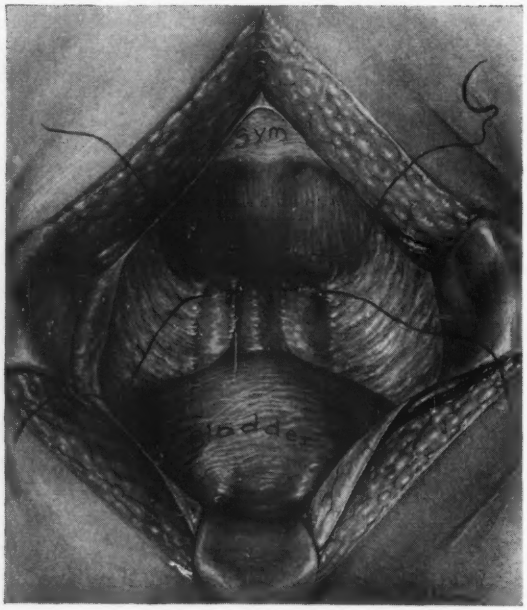

Fig. 2.—A drawing representing the wide exposure of the field of operation and the manner in which a suture is carried into the vaginal wall lateral to the urethra and secured to the periosteum of the pubis. The illustration does not show the double bite into the vaginal wall which is recommended to obtain a more secure hold.

Comments and Conclusions

After 12 years of experience with simple vesicourethral suspension, it is fully realized that the procedure is by no means a panacea for urinary stress incontinence in the female. It is believed, nevertheless, that over this period of time it has proved to be a valuable adjunct to the number of operations which have been devised and modified for the correction of stress incontinence.

The clinical data which were accumulated from a series of 132 patients are especially valuable, it seems, since they are surveyed over a relatively long-term view. Only 4 patients were lost to follow-up in this study.

About one-half of the patients had a vesicourethral suspension for stress incontinence as a primary procedure. At first glance, this choice may appear to be too liberal. It is felt, however, that a justifiable indication was present at the time. As our experience continues to grow, the selection of the operation as a primary procedure may become more restricted.

It is well to re-emphsize that the diagnosis of urinary stress incontinence is not always easy. A searching history, a complete urinalysis, endocystoscopy, and the preoperative "stress" test are mandatory in a properly conducted diagnostic work-up.

The results of the operation show an over-all successful outcome in 84 per cent of the cases. This incidence is considered creditable when the results are compared with those obtained from the use of other techniques. It is felt that the value of our results is enhanced by a comparatively long period of observation and also by the results that have been published by others[3, 14-17] who have used the operation (Table III).

TABLE III. COMPOSITE INCIDENCE OF FAILURES FROM PUBLISHED REPORTS

	NO. CASES	FAILURES	PER CENT
Marshall, Marchetti[1]	132	21	16.0
Chalmers[14]	30	1	3.3
Gallaher[15]	11	1	9.1
Gillam, Hunter, and Darner[16]	20	1	5.0
Jeffcoate and Roberts[19]	19	2	10.5
Ullery[3]	24	2	8.3
Total	236	28	11.8

One of the primary indications for vesicourethral suspension is its use in cases where standard vaginal procedures have failed to correct stress incontinence. The re-evaluation of our failures, especially the late recurrences, indicate that in the presence of extensive vaginal fibrosis and scarring vesicourethral suspension alone will not suffice. Ball's approach to this type of case, it is thought, is a better choice. In addition, faulty technique and other ill-chosen cases were responsible for some of the earlier failures.

As the complications are reviewed, it may be stated that up to the present time they have not carried with them any serious implications.

The technique has been altered little, and because of its relative simplicity it is favored over other more complicated procedures.

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Obstetrics

FACTS PERTINENT TO THE ETIOLOGY OF ECLAMPTOGENIC TOXEMIA*

A Summation of Previous Observations (1930-1955)

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IN A search for the cause of eclamptogenic toxemia, it is fortunate if one happens to find what appears to be a significant piece in the jigsaw collection of phenomena pertaining to this disease. Onto this piece, if it be really significant, other pieces of the puzzle logically fit or pointedly suggest other pieces needed to fill in deficiencies. In this manner, just as a jigsaw puzzle becomes more workable with further additions, so may the mechanism of development of pre-eclampsia, eclampsia, and abruptio placentae begin to take form. Additional needful data can then be purposely and not accidentally supplied.

In recent years, attention has been focused on the probabilities that (1) *placental necrosis* and (2) *vascular spasm* play primary roles in the genesis of this disease.

1. Placental Necrosis

In 1930, one of us (R. A. B.) came to be impressed with the finding of what appeared to be areas of recent degeneration on the maternal surface of placentas, especially from cases of abruptio. Here was a finding more suggestive of cause than effect since it represented degenerating tissue in contact with the intervillous maternal blood stream, offering possibilities of dissemination of breakdown products of probable toxicity into the general circulation.

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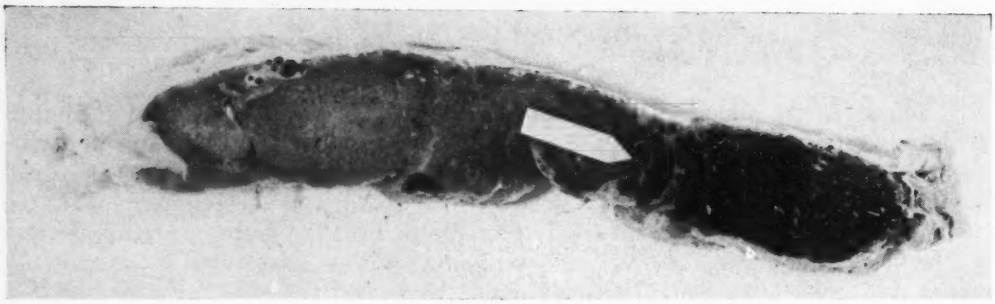
Thenceforth, a systematic gross and microscopic examination of formalin-fixed placentas from both normal and toxic patients was undertaken and correlated with the clinical findings. It soon became apparent that areas of degeneration were conspicuously frequent in placentas from toxic patients (85 to 90 per cent) and impressively infrequent in those from normal patients.[1] To be sure, there was a variety of lesions, but with emphasis on those showing gross and microscopic evidence of acute placental necrosis. By correlation with the clinical history it was possible to recognize and label specifically those which were slow forming and nonspecific for toxemia, designated "A" (white) and "B" (yellow), and those which were more acute and specific for toxemia, designated "C" (yellow brown), the more acute "D" (brown), and the most acute "E" (black).

The specificity of the acute types of placental infarction for pre-eclampsia and eclampisa has been verified and well illustrated by Patterson, Hunt, and Nicodemus,[2] Falkiner,[3] Steigrad,[4] and more recently by Thomsen.[5, 6] Failure of other investigators to verify these findings can usually be ascribed to examining fresh rather than formalin-fixed placentas[7] or checking by erroneous standards.[8, 9] The lesions in fresh placentas are much obscured by blood. The criteria by which areas of acute placental infarction may be recognized in formalin-fixed placentas, both grossly and microscopically, have been described in detail in previous publications.[1, 10, 11] Familiarity with these criteria is of some aid if one must select acute lesions in fresh placentas.

A study of the literature prior to 1930 disclosed that Young,[12] in 1914, had recognized these lesions and emphasized the consistency of these findings in placentas from toxic patients. He concluded, however, that the lesions were the result of abnormalities in the maternal and not the fetal circulation—a conclusion which one cannot reconcile with the structure of the placenta and the course of the maternal and fetal components of its circulation, as will be described farther on.

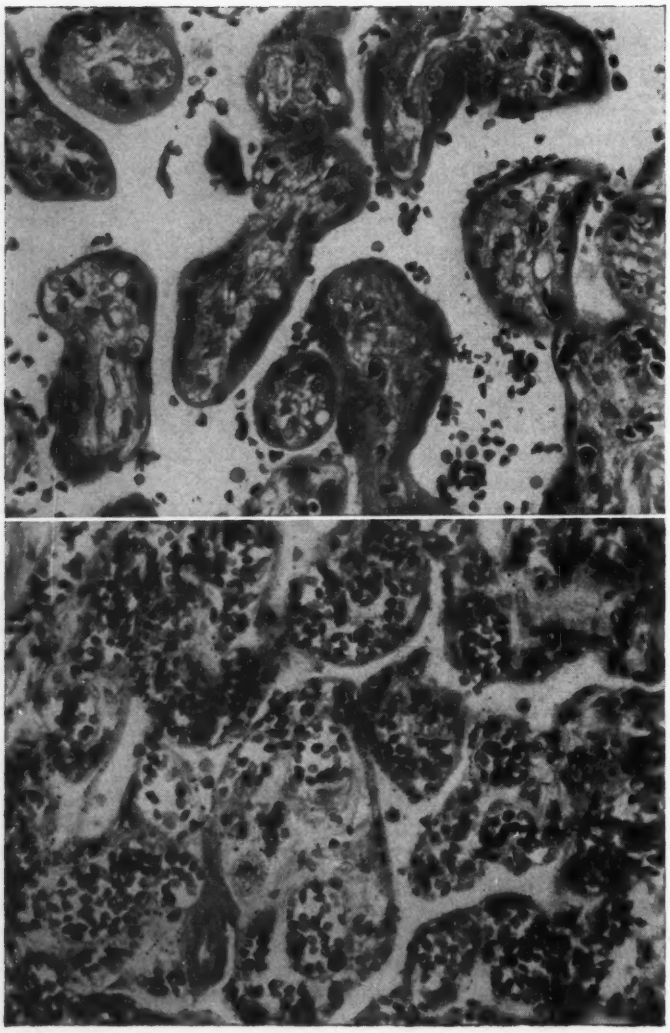
Failure to obtain more than 85 to 90 per cent correlation between a clinical diagnosis of toxemia of pregnancy and the placental findings was first thought to be explained in part by the obvious possibility that toxemia may have developed between the date of the last prenatal visit and the onset of labor. Cases illustrating this possibility could now and then be found. An additional and more important explanation of the 10 to 15 per cent deficit of complete correlation was found in the discovery that proteinuria of a very significant degree occasionally developed during labor.[11] In a series of patients in whom the urine and blood pressure were normal on admission to the hospital in labor, proteinuria ranging from 2 to 4 plus was found to be present at delivery with a frequency of 10 per cent and to a lesser degree in 41 per cent. This finding was soon verified by Douglas[65] and more recently by Morton and Chesley.[13] In some of these patients an appreciable rise in diastolic pressure developed at the end of labor or during the first day after delivery. Since 49 per cent of the patients failed to develop proteinuria during labor, the physical strain of labor could not be implicated as a causative factor, inasmuch as exertion must have been the same in each group.

Examination of the placentas showed characteristic dark, well-delineated areas of acute "E" infarction (Fig. 1, *A*). In general, the strips from these placentas appeared much darker than normal. As will be explained farther on, one could not escape the impression that the factor which initiated labor (hormonal?) may also have initiated a mechanism by which acute placental infarction developed and caused a very transient and seldom recognized period of intrapartum toxemia.



A.

B.



C.

Fig. 1.—*A*, Strip of formalin-fixed placenta from a case of acute toxemia initiated during labor. Normal urine and blood pressure (110/70) on admission early in labor. Blood pressure 116/90 and flocculent proteinuria at delivery. One half of maternal surface of placenta appeared black—acute "E" infarction. Blood pressure and urine returned to normal within two days.

B, Microscopically the light normal portion of the placenta shows (1) open intervillus spaces, (2) villi of normal size, (3) villus capillaries of normal size (width of 1 to 3 red cells), and (4) light-staining, intact nuclei of chorionic epithelium.

C, The black acute "E" infarcted portion shows (1) narrowed or obliterated intervillus spaces, due to (2) enlarged, crowded villi, due to (3) distended villus capillaries (10-20 red cells), and (4) dark-staining (pyknotic) and fragmented (karyorrhexic) nuclei of chorionic epithelium.

Toxemia of Pregnancy Presents Specific Placental Pathology.—It is thus possible to examine a numbered but unnamed placenta which has been fixed in 10 per cent formalin for three to four weeks, then cut it in strips 1 cm. in width, and ascertain whether or not the patient's pregnancy was complicated by toxemia.[1] It is usually possible to state whether the toxemia was gradual or acute or whether it manifested itself as abruptio.

Occasionally convulsions may occur during or shortly after labor, accompanied by little or no proteinuria or rise in blood pressure. Epilepsy is apt to be suspected rather than eclampsia. In such cases, examination of the placenta apparently offers the only means of diagnosing or ruling out toxemia of pregnancy.[14] Up to the present time obstetricians and pathologists have not recognized the value of this knowledge as a means of affirming or denying the presence of true toxemia of pregnancy and differentiating hypertension of true toxemia from that of uncomplicated hypertensive vascular disease.

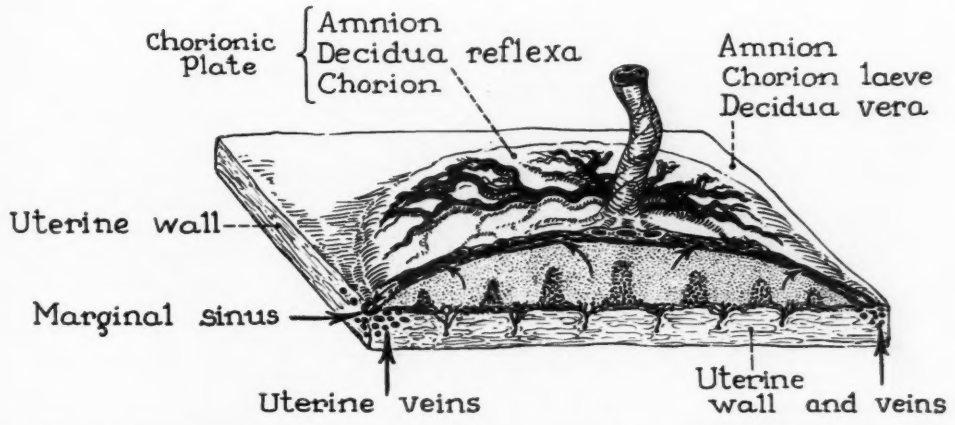


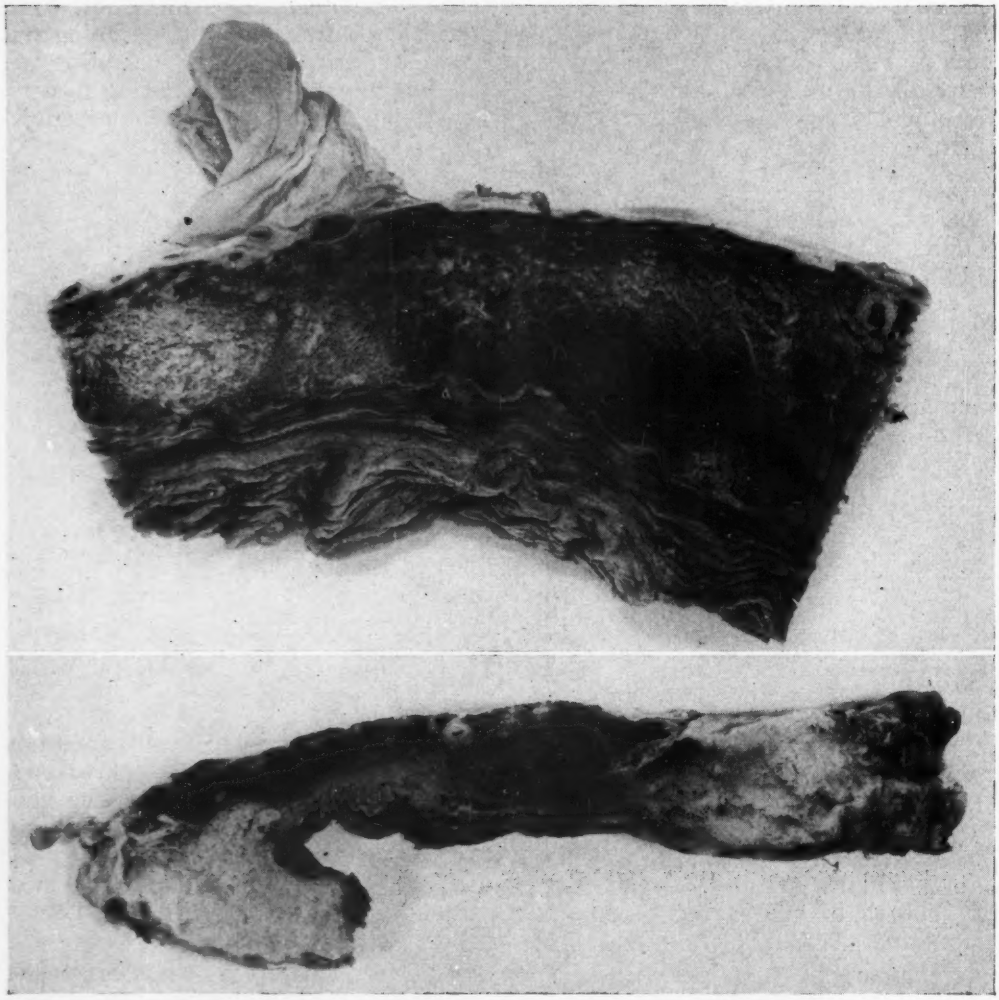
Fig. 2.—Diagrammatic representation of the course of the maternal blood, discharging from decidual arterioles into (1) intervillus spaces to subchorionic plate, thence (2) peripherally to margin of placenta, into (3) marginal sinus, thence (4) through communications into uterine veins, and (5) returned to the general circulation.

Mention has been made that many writers consider placental infarction the effect rather than the cause of toxemia of pregnancy. This view postulates that placental necrosis is the result of an unknown toxin present in the maternal circulation. According to a more favored viewpoint it is considered the result of ischemia of the placenta due to atherosclerosis or narrowing of the decidual arterioles. A consideration of the structure of the placenta and the course of the maternal intervillus circulation renders these viewpoints untenable.

Course of the Maternal Intervillus Circulation.—The placenta is composed of cotyledons partially separated by decidual septa. The latter do not extend more than two thirds of the distance from the decidua to the chorionic plate, thus leaving a loose uninterrupted meshwork of villi beneath the chorionic plate which permits circulatory intercommunication among all cotyledons. Therefore, the cotyledons are not to be considered completely compartmented units each with its own independent inflow and outflow of maternal blood. The sinusoidal circulation of maternal intervillus blood, supplied by decidual arterioles, is constantly impelled by the maternal blood pressure to ascend to the chorionic plate at which level it must change direction and move peripherally to the margin of the placenta (Figs. 2, 3, *A* and *B*).

At this point the placental chorion, decidua reflexa, and amnion extend over the margin of the placenta and become the chorion laeve, decidua vera, and extraembryonic amnion, respectively, adhering to the uterine wall, and blocking further peripheral spread of the maternal blood, thus forming a pseudochannel, the marginal sinus, around the border of the placenta (Fig. 3, *C*). Communications are developed between the marginal sinus and the underlying uterine veins,[15, 16] which return the blood to the general circulation.

A.



B.

Fig. 3.—*A*, "In situ" strip of placenta, showing course of dark maternal blood stream beneath chorionic plate. Uterine muscle below.

B, Strip of placenta from a case of abruptio, showing thromboplastin-induced "in situ" thrombosis of subchorionic maternal blood stream. The acutely infarcted area lies between the two light areas; the thrombosed maternal blood stream lies beneath the chorionic plate near the left end of the strip.

It is held by Romney[17] that the decidual septa carry functioning maternal arterioles high into the placental substance, permitting discharge of blood into the upper intervillus spaces, from which level it courses downward to leave

the placenta by decidual veins at the deciduoplacental junction. Sections of formalin-fixed placental tissue taken at various levels parallel to the placental attachment of an "in situ" placenta (Fig. 3, *A*), and transecting the decidual septa, do not support this concept. By way of differentiation, villus stems are characterized by a chorionic epithelial covering, a fibrous and muscular stroma, and the presence of functioning villus vessels. Decidual septa are characterized by absence of epithelial covering, presence of decidual cells embedded in a homogeneous hyalinelike substance, and absence of functioning vessels. Nonfunctioning "ghost" vessels showing hyalinized wall and amorphous debris within the lumen may be seen (Fig. 4). It does not appear, therefore, that maternal blood is discharged from the summit of decidual septa to course downward to the decidual base and find its way out of the cotyledon by maternal venous openings in the decidua. Since maternal decidual arterioles also discharge blood into the deciduoplacental zone, a dual blood supply would produce paradoxical movements of arterial blood simultaneously in opposite directions.

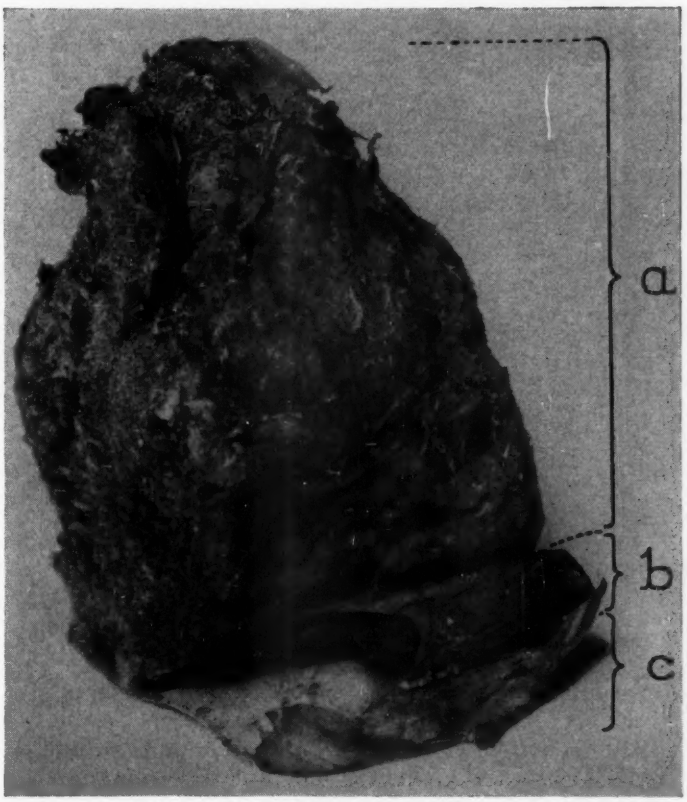


Fig. 3.—*C*. Section from border of placenta (*a*), showing membranous marginal sinus and the contained thrombus (*b*), and the reflected portion of membranous outer wall (*c*).

Furthermore, injection of a fresh specimen of uterus containing the "in situ" fetus and placenta shows that colored material injected into the uterine arteries proceeds from decidual arteries through intervillus spaces to the chorionic plate, thence peripherally to the marginal sinus, returning to the general circulation by way of communications with the uterine veins. Material injected into the uterine veins follows the reverse of this course.[15, 18]

Should it be possible for any decidual arteriole to become blocked by atherosclerosis or other obliterative process, the dependent villi could still be supplied by the subchorionic blood stream, although blood at this level would probably be of inferior quality.

Therefore, in view of the course of the placental circulation, a necrotizing factor contained in the maternal blood must necessarily affect the entire placenta and produce generalized necrosis. On the contrary, examination of placentas in cases of pre-eclampsia and eclampsia has shown that necrosis is preponderantly of a localized character limited to the distribution of one or more obstructed villus veins, as shown by greatly dilated villus capillaries, enlarged crowded villi, and diminished or obliterated intervillus spaces over the area of distribution of the blocked vein. This furnishes the only explanation of the fact that villi which are normal in every respect are found bordering on enlarged crowded necrosing villi of an adjacent infarcted area with no intervening decidual septum. The nearest approach to over-all complete involvement of the placenta with acute infarction is seen in placentas from cases

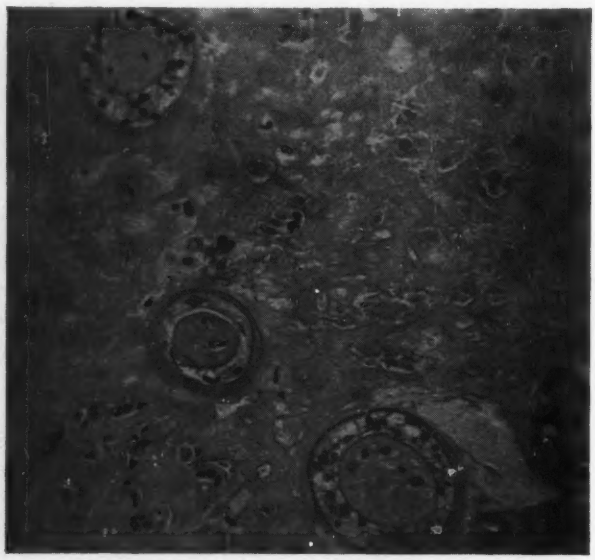


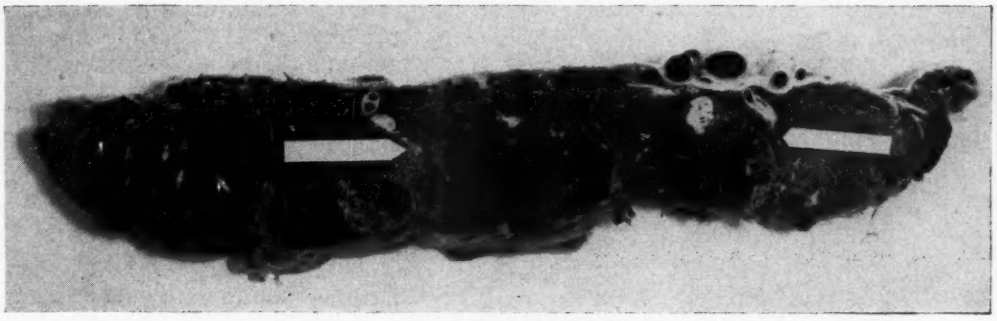
Fig. 4.—"Ghost" nonfunctioning maternal vessels in a decidual septum of an "in situ" placenta.

of fulminating abruptio (Fig. 5, *A* and *B*), and toxemia initiated during labor (Fig. 1, *A*, *B*, and *C*, and Fig. 11, *A* and *B*) which appear black with acute "E" infarction throughout most if not all of the placental strips. In these cases the widespread spasms involving the vessels on the fetal surface of the placenta lead one to believe that the sphincters of practically all placental veins on the surface or in the placental substance are in a state of spasm.

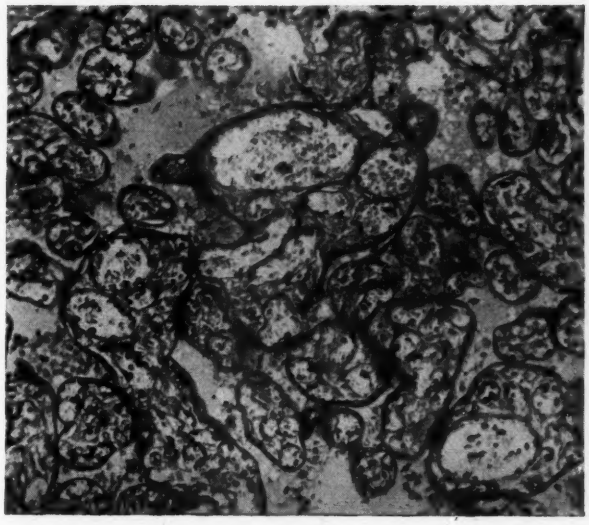
2. Vascular Spasm

Mechanism of Placental Ischemia and Infarction.—Some have questioned the appropriateness of the term "infarct" when applied to areas of villus necrosis. An area of necrosis of placental tissue resulting from occlusion of a fetal placental vein with resulting enlargement of dependent villi, diminution of the intervillus blood spaces, and thrombosis of its intervillus maternal blood supply, is qualified to be termed an "infarct" as truly as is an area of necrosis of the lung, deprived of its arterial blood supply by an embolic process, as the mechanism will show.

In an early stage of this study, it was postulated that thrombosis possibly resulted from the impact of vigorous fetal movements on exposed fetal vessels on the surface of the placenta. Later on the discovery of subendothelial fat cells suggested the possibility of atheromatous change and thrombus formation in fetal placental vessels. Neither of these theories could be sustained by convincing evidence of sufficient blockage to account for infarction and were therefore abandoned.



A.



B.

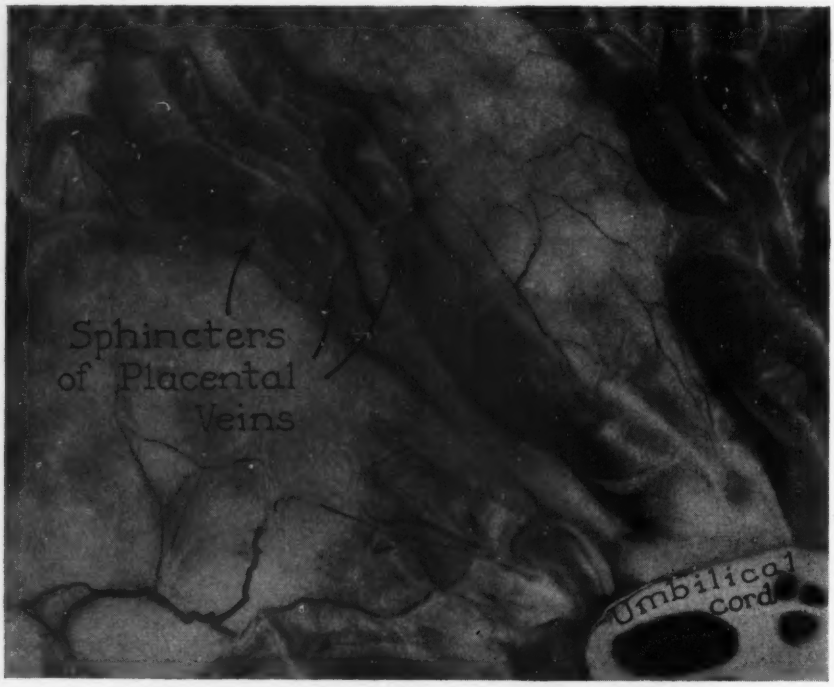
Fig. 5.—A, Placental strip from case of superimposed fulminating severe abruptio involving entire placenta, except at extreme right, with acute "E" infarction. Prenatal visit near term showed blood pressure 135/85 and a trace of proteinuria. Twelve hours later, severe hemorrhage, abdominal pain, blood pressure 160/100, flocculent proteinuria, followed by shock. Spontaneous rapid labor, stillborn baby; 2,000 c.c. blood loss; transfusions; recovery.

B, Microscopically, distended capillaries causing enlargement and crowding of villi; narrowing or obliteration of intervillus spaces; anoxic necrosis of chorionic epithelium; thromboplastin-induced intervillus and subplacental thrombosis with abruptio.

Spanner's[15] researches on the placental circulation furnished a significant clue to the manner in which placental infarction occurs. By serial sections and injection methods he demonstrated not only the path of the intervillus maternal circulation and existence of the marginal sinus, but also the presence of definite sphincters in the fetal collecting veins both in the substance and on the fetal surface of the placenta.[15, 16] This has readily been verified in placentas we have examined (Fig. 6, *A*, *B*, *C*, and *D*).

The physiological function of these sphincters is not definitely known, but if they are susceptible to a humoral spasmogenic hormone, the exit of blood from the corresponding placental unit must be greatly impeded or completely obstructed. If the placenta from a toxic patient is inspected on its fetal surface *immediately* after the third stage, spasms of both arterioles and veins appear to be very numerous (Fig. 7, *A*), as compared with those of the placenta of a patient who had neither ante- nor intrapartum evidence of toxemia.

Delayed spasm of fetal arteries and/or veins seen on the surface of the placenta after delivery is generally considered to be of little significance and is attributed to anoxia of the vessels following separation of the placenta.

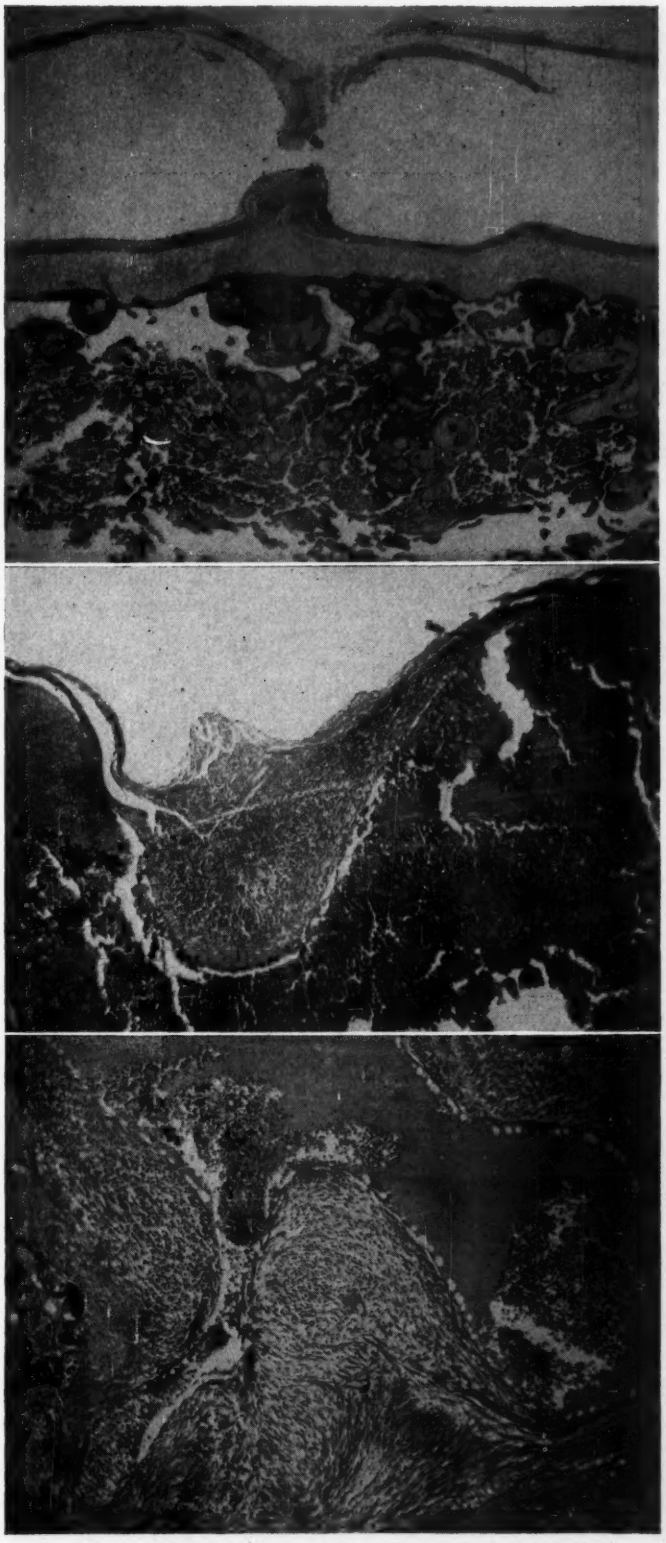


A.

Fig. 6.—*A*, Sharp constrictions in fetal placental veins indicate sites of venous sphincters. *B*, Section through fetal vein sphincter showing marked narrowing of lumen, indicating possibilities of obstruction to exit of blood from corresponding placental unit. *C*, Section through fetal vein sphincter, showing inner layer of longitudinal muscle fibers bordering on lumen and transversely cut circular muscle fibers of body of sphincter. *D*, A chance demonstration of a fetal vein sphincter in the substance of the placenta, showing transversely sectioned circular muscle fibers.

By way of investigating this impression, 100 placentas were inspected for spasms at the end of the third stage. Nine were rejected, examination having been delayed and not immediate. Fifty-six placentas (61 per cent) showed no vascular spasms. In 6 (10 per cent) of these, there was mild to moderate evidence of ante- or intrapartum toxemia. Hidden spasm within the placental substance remained a possibility. Thirty-six placentas showed vascular spasm. Twelve, or 33 per cent, of these showed mild to moderate evidences of ante- or intrapartum toxemia. A larger series would have been desirable.

Since the fetal heart continues to force blood into the obstructed units, the villus capillaries become greatly engorged and distended with resulting enlargement and crowding of villi, diminution or obliteration of the intervillus spaces, and exclusion of the maternal intervillus circulation on which



B.

C.

D.

Fig. 6.—*B*, *C*, and *D*. *(For legend see opposite page.)*

the vitality of the chorionic epithelium depends. Necrosis of the epithelium ensues, as may be readily recognized by pyknosis, karyorrhexis, and ultimately karyolysis of the nuclei (Fig. 1, *C*, and Fig. 10, *B*). This process represents an indirect form of infarction in which the adequacy of the maternal intervillus arterial channels is entirely dependent on and affected by the size of the villi which, in turn, is dependent on the degree of spasm and blockage at the site of fetal vein sphincters. The hydropic hydatidiform villi and the edematous erythroblastotic villi, by virtue of their enlargement and crowding, occasionally produce the same effect, which may result in toxemia.

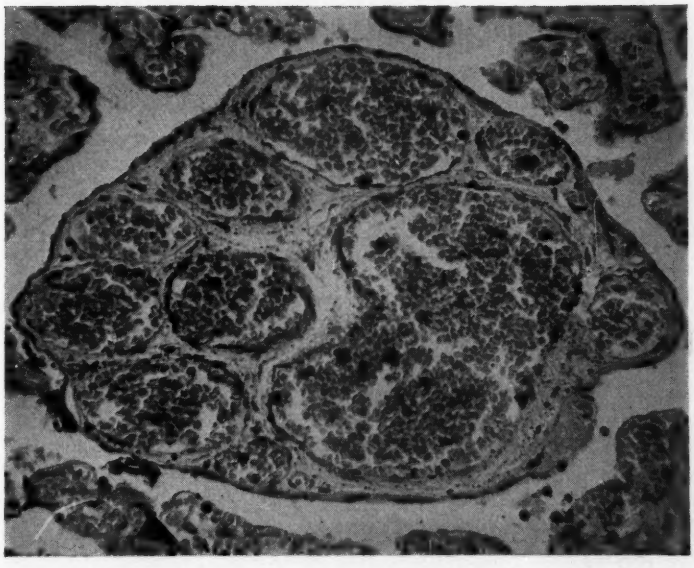
Grossly, the placenta in the acutely infarcted area appears somewhat thicker because of enlargement of the innumerable individual villi; also much darker because of thrombosed intervillus and intracapillary blood due to necrosis of chorionic epithelium and villus capillary endothelium and more or less stasis of the circulation in the area. The so-called "red infarct" derives its name from the fact that distended villus capillaries often rupture, the extravasated fetal blood forming a clot within the infarct due to incompatibility with maternal blood or thromboplastin effect. Actually, the infarct itself is black, since the blood it contains has been thrombosed and changed to a dark color for some time before expulsion of the placenta. The most extensive infarction is found in placentas of patients with acute severe abruptio (Figs. 5, 8, and 10) or of those who develop toxemia during labor (Figs. 1 and 11). Such extensive infarction implies multiple sphincter involvement. Acute pre-eclampsia and eclampsia are characterized by localized black areas of "early E" or slightly shiny "late E" infarction implying lesser sphincter involvement; a sustained state of pre-eclampsia may be associated with "D" infarction of a brown color due to changes in the hemoglobin; "C" infarction is of a gray-brown color and of still longer duration consistent with a milder pre-eclampsia of slow development probably from single partial sphincter occlusion; "B," of yellow and "A" of white color are nontoxic infarctions apparently due to a slow obliterative process in the corresponding fetal artery (Fig. 9), which gradually induces thrombosis and hyalinization of the intervillus blood and produces "ghost villi."[1] Absence of engorgement and distention of the capillaries in the "ghost villi" indicates that the process was slow, nontoxic, and not initiated by spasm of the sphincter.

Zeek[19] has described pale, round or oval areas in the placenta occasionally present in the toxic cases (Fig. 10, A), to which she has applied the term "nodular ischemia" from the fact that the villus capillaries show a much lessened content of blood. There is no distention of the villi, the intervillus spaces are of normal size, and the chorionic epithelium and capillary endothelium show no signs of necrosis. It is our belief that localized spasm of a fetal placental arteriole (Fig. 7, *A*) accounts for the areas of "nodular ischemia." In other words, the area of nontoxic anemic "nodular ischemia" is the antithesis of the toxic congested "E" and "D" infarcts which originate in spasm of the venous sphincter. It is probable that the spasmogenic agent responsible for each type is the same.

Nature of the Spasmogenic Factor Which Initiates Acute Infarction.— From what has been stated thus far, it is apparent that spasm of the fetal vein sphincter is the logical and probable initiator of placental infarction of the acute and subacute type. In turn, sphincter spasm must be triggered by a spasmogenic agent. Since initiation of toxemia is highest during labor, the thought suggests itself at once that the agent which initiates rhythmic contractions of the uterine muscle may well be responsible for spasm of the fetal vein sphincters and thereby cause acute and subacute placental infarction. It is an accepted fact that labor complicated by abruptio or eclampsia is usually

characterized by frequent severe pains and rapid progress as if stimulated by an excess of Pitocin. Although labor may be initiated by mechanical means, the fact remains that oxytocin is outstanding in its ability to produce

A.

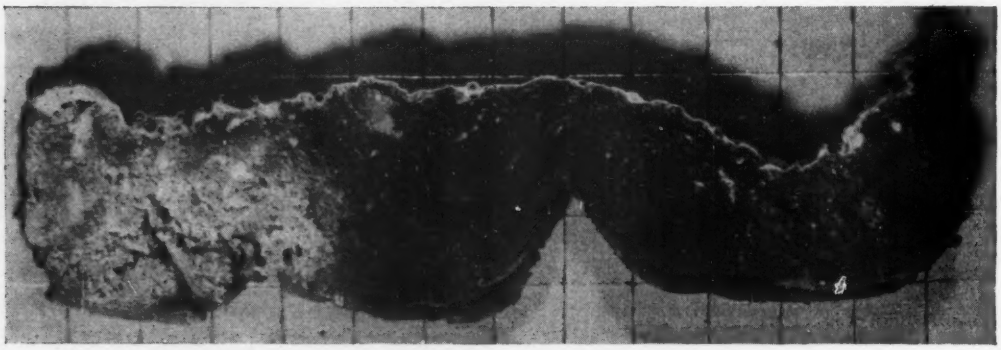


B.

Fig. 7.—*A*, Appearance of fetal surface of placenta from a case of eclampsia. Excessive involvement of fetal placental veins and arteries with spasms as noted immediately after expulsion of placenta and promptly photographed. Arteries are smaller and override veins.

B, Note typical effect on size of villus and capillaries and the pyknotic fragmented nuclear material of the chorion and capillary endothelium. (Unfortunately, a placental strip was not photographed.)

rhythmic uterine contractions and initiate or stimulate labor. When injected in dilute strength into the surface veins or arteries of a freshly delivered placenta, it induces marked localized and elongated venous spasms and elongated arterial spasms very similar to those seen in a freshly delivered placenta of a severely toxic patient.



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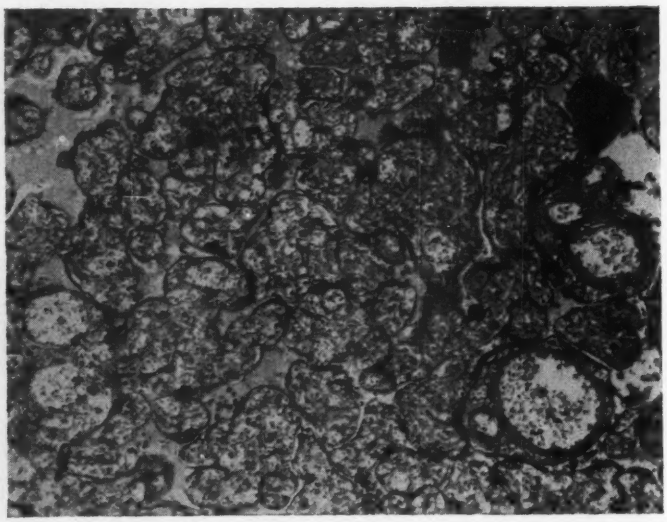


B.

Fig. 8.—*A*, Placental strip from case of severe abruptio which developed during labor. Stillbirth and excessive hemorrhage. Recovery. Black portion is early "E" infarction. Light portion is normal.

B, Microscopically, enlargement and crowding of villi due to distended capillaries; thrombosis in intervillous spaces.

With the advent of pregnancy the interrelationship of hormones of the pituitary, ovaries, and adrenal glands becomes even more complex by the addition of placental substances, namely, gonadotrophic hormone,[20] adrenocorticotrophic hormone,[21] adrenocorticosteroids,[22] estrogen,[23] pitocinase,[24] progesterone,[25] and acetylcholine.[66] A placental source of estrogen and progesterone is indicated by the fact that castration of pregnant women during the second and third trimesters of pregnancy does not prevent an increase in these hormones.[26]

Pituitary Gland.—It is significant that the pituitary gland doubles in size during pregnancy.[27] Increase in an antidiuretic substance during pregnancy[28] may well be a manifestation of increased activity of the posterior lobe. The increase in pitocinase[24] may also indicate a response to increased activity of the posterior lobe. Although Pitressin is characterized by its pronounced vascular effects, it also exerts definite oxytocic effect.[29] The gonadotrophic activity of the pituitary is little or absent during pregnancy.[30] Byrom[31] found that a tenfold increase in sensitivity to Pitressin was manifested by priming with estrogen.

Adrenal Glands.—Toxemia of pregnancy is known to occur in the presence of Addison's disease.[32] Jailer[68] demonstrated the presence of corticosteroids in the placenta of an Addisonian patient. The adrenal glands hypertrophy in pregnancy, conceivably from stimulation by the increasing level of estrogen or as a response to excess stimulation by placental adrenocorticotrophic hormone or by the anterior lobe of the pituitary gland. The excretion of urinary corticoids has been found to show a fourfold increase in the third

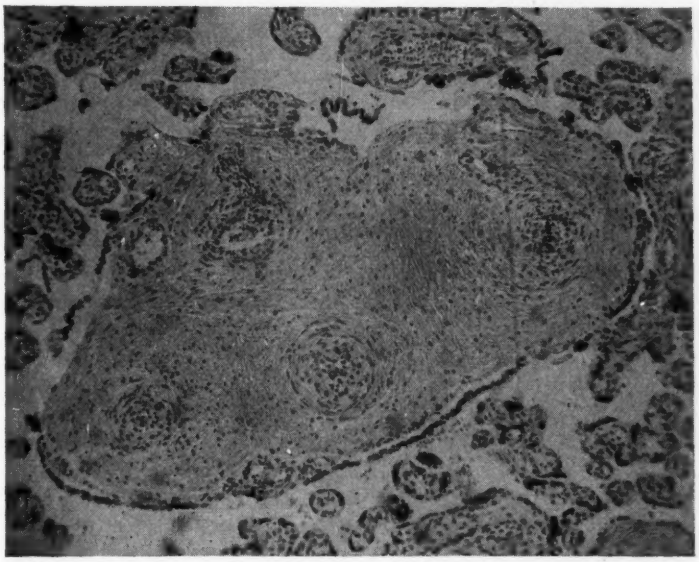
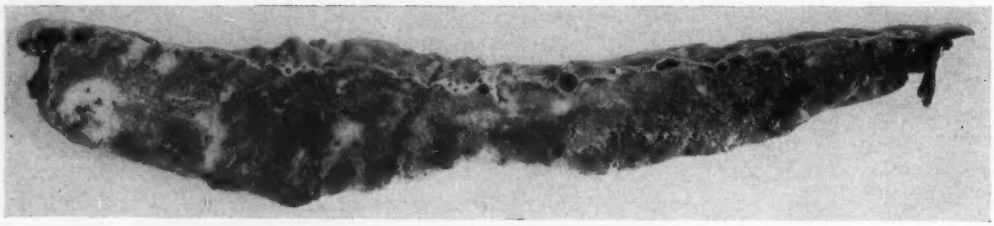


Fig. 9.—Obliterative process in fetal placental arteries, producing slow, white, firm infarction of "A" type.

as compared with the first trimester.[33] Twenty-five per cent of the corticoids excreted in the third trimester were of the desoxylike compound,[34] which influences water and electrolyte metabolism and exerts hypertensive effect.[35, 36] In this mechanism, salt in the arterial walls plays an important role.[37] The desoxylike steroids have been found to be significantly elevated in severe toxemia.[34] The total corticoid excretion in toxemic women in the third trimester has been found to be almost twice as high as that of normal women.[34, 38] The urine of toxemic patients contains abnormal amounts of desoxycorticosterone-like sodium-retaining substance.[39] The experimental administration of desoxycorticosterone to animals and man produces a gradual rise of blood pressure,[35, 36] in the mechanism of which salt plays an important part. The simultaneous administration of salt and desoxycorticosterone distinctly increases the pressor effect of the latter,[40, 41] whereas salt deprivation lessens it.[42] Apparently any pressor action of sodium chloride is dependent

upon support by the adrenal mineralocorticoids.[43] It has been demonstrated that the arterial walls of hypertensive individuals contain abnormally large amounts of sodium.[37] Adrenalectomy is followed by hypotension in normal animals and in those with renal[44] or centrogenic forms of hypertension.[45] Likewise, the pressor response to epinephrine,[46] norepinephrine,[47] Pitressin,[46] renin,[48] VEM[49] and nervous stimulation, is reduced after adrenalectomy.[50]

Estrogen.—Estrogen increases during pregnancy from the twelfth week on to delivery.[50] Cohen[51] found that estrogen (estriol) is excreted in the urine in a conjugated inactive form during pregnancy, whereas active free estrogen increases shortly before labor. Synergism has been demonstrated between free estrogen and the oxytocic principle of the posterior pituitary. Excess estrogen causes hypertrophy of the adrenals[52] and induces water and sodium retention.[37, 53] It is believed that estrogen conditions the maternal vascular system for more intense action on the part of the corticoid hormones.[54]



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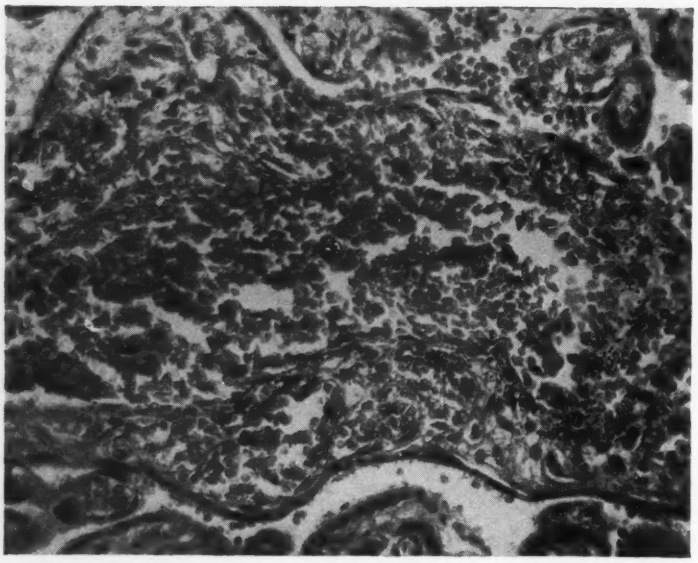


B.

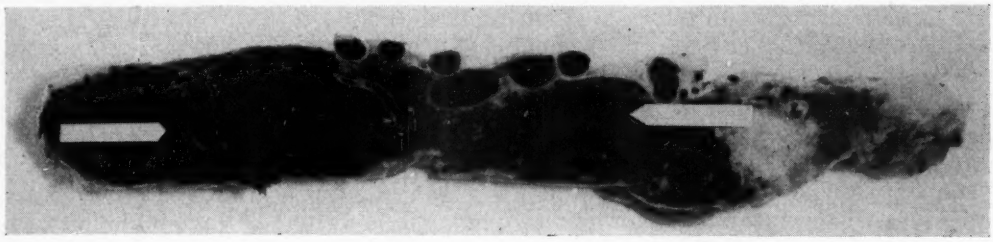
Fig. 10.—*A*, Placental strip from a case of fulminating abruptio; acute "E" infarcted areas beneath depressed area in center of maternal surface. "Nodular ischemia" (Zeek), white area at extreme left.

B, Microscopically, marked enlargement of villus due to distended capillaries; pyknosis and karyorrhexis of capillary endothelium due to trauma of stretch; fragmented nuclear material may be seen around the periphery of distended villus vessel, especially along right border; pyknosis of chorionic endothelium due to stretch and anoxia.

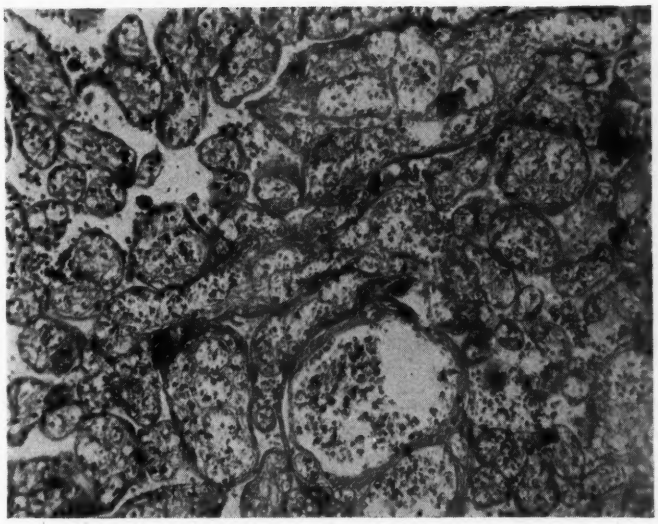
Progesterone.—Progesterone is increased coincidentally with conception and gradually increases to a peak two to three weeks before delivery. Thereafter it declines up to delivery.[25, 55] It is antagonistic to estrogen and also to Pituitrin (Knaus[56] reaction). Haskins[57] found that the progesterone content

of normal placental tissue after spontaneous labor was apparently only one fourth of the amount obtained from the placenta at cesarean section before labor had begun. It has been shown that pregnanediol excretion diminished prior to false labor, then increased for a time, but subsequently fell at the onset of true labor.[53] Snyder,[58] by artificially increasing the supply of progesterone through inducing ovulation in the rabbit near term, was able to prolong pregnancy and demonstrate complete resistance to administration of Pituitrin.

From the foregoing collection of data pertaining to the behavior of the hormones especially concerned in pregnancy, it appears that oxytocin is held in abeyance during pregnancy by acetylcholine, progesterone, and pitocinase.



A.



B.

Fig. 11.—*A*, Severe prelabor toxemia: blood pressure 190/110; proteinuria 2 plus, increasing to 4 plus at delivery. Total acute "E" infarction of the placental strip except for light round area of Zeek "nodular ischemia" at right end of strip.

B, Microscopically, characteristic appearance of enlarged crowded villi and distended capillaries, apparently due to generalized spasm of placental vein sphincters, causing obstruction of maternal intervillus circulation. Higher power would show pyknotic fragmented nuclei of capillary endothelium and chorionic epithelium.

Gradually, but at times precipitously, it appears, oxytocin is released from its inhibiting factors near term by a drop in progesterone and conjugated estrogen; also, the uterine muscle is sensitized to the action of Pitocin and Pitressin by the presence of free estrogen at term. Meanwhile the mineralocorticoids increase in the third trimester, sensitizing the vascular system to the effect of Pitressin with the result that arterioles and precapillary vessels decrease in caliber, as may be noted by ophthalmoscopic examination in the ninth month of pregnancy.[59] Landesman and Douglas[60] have demonstrated this vascular

phenomenon in the bulbar conjunctival vessels late in pregnancy. The uterine muscle, reacting at first in a haphazard ineffective rhythm (false labor), eventually responds to the increasing oxytocic stimulus and assumes a rhythm of effective labor. Govan[61] found that the urine of a toxemic woman contained a substance which causes experimental animals to become highly sensitive to Pituitrin.

It is conceivable that the placental fetal vessels and venous sphincters may, in a similar manner, become sensitized to the action of Pitressin and Pitocin, which, by increasing the tendency to spasm, increases the liability to toxemia as term approaches, reaching a maximum effect during labor (Fig. 11, *A* and *B*). It seems that the measure of a pregnant patient's susceptibility to toxemia could lie in the titer of her uninhibited blood oxytocin plus the degree of priming of the placental venous sphincters brought about by estrogen, desoxycorticosterone, and salt sensitization.

The Noxious and Lethal Components of Placental Necrosis.—Thus far it can be asserted that (1) true toxemia of pregnancy (abruptio, pre-eclampsia, and eclampsia) is characterized by a specific placental pathology (acute and subacute placental infarction) and (2) that the gross and microscopic characteristics of the infarction can logically be explained by a spasmogenic hormone (oxytocin ?) acting upon one or more of the venous sphincters present in the fetal veins of the placenta.

Vascular Spasm.—If vascular spasm, per se, becomes generalized in the course of either primary or superimposed toxemia, it is capable of producing damaging ischemic effects on vital organs or vulnerable tissues. If arteriolar retinal spasms are a dependable measure of their presence elsewhere in the body, spasm is not a serious factor until toxemia becomes severe. This is more likely in superimposed toxemia. There is a gradual increase in pre-existing hypertension of hypertensive vascular disease in the eighth and ninth months, apparently due to increased secretion of desoxycorticosterone and retention of salt, but unassociated with appearance of retinal spasms, significant degrees of proteinuria, or clinical symptoms of toxemia. It is generally recognized that these patients are particularly prone to develop sudden exacerbation of hypertension, proteinuria, and clinical symptoms of toxemia—superimposed toxemia—which probably results from sudden spasm of the placental vein sphincter of oxytocic (?) origin. It is under these circumstances that retinal spasms become pronounced. Marked exacerbation of blood pressure occurs along with heavy proteinuria and significant clinical symptoms. This sudden change is associated with extensive acute "E" infarction, which strongly suggests the liberation of a spasmogenic factor from placental degradation or serotonin rather than from corticoid effect. Under these circumstances, the presence of arteriolar spasms in the kidneys may induce liberation of another hypertensive agent, renin. Kidney damage, oliguria, or shutdown may ensue as one of the most serious effects of spasm, along with ADS effect, but is a secondary and not a primary factor in the etiology of the disease.

Thromboplastin.—Apparently this enzyme is one of the first products of placental necrosis. It probably results from the trauma of stretch and anoxia affecting the chorionic epithelium and the endothelium of the greatly dilated villus capillaries. Placental tissue and particularly decidual tissue are known to be unusually rich sources of thromboplastin which initiates clot or thrombus formation by a several-stage process of (1) formation of thromboplastin from tissue injury, (2) conversion of prothrombin to thrombin by addition of calcium and thromboplastin, (3) formation of fibrin by action of thrombin on fibrinogen.

The following case illustrates the rapidity with which this process may produce abruptio placentae.

Mrs. G., aged 30 years, gravida ii, para i, following a period of painful Braxton Hicks contractions in the thirty-first week of her first pregnancy, developed abruptio placentae and was delivered of a stillborn baby. The present pregnancy was likewise complicated by frequent Braxton Hicks contractions in the sixth and seventh months. In the thirty-first week, at a regular prenatal visit, at 2:30 P.M., her blood pressure was 120/70, and the urine showed no proteinuria. Subjectively there were no symptoms of toxemia. Three hours later, at home, she developed constant abdominal pain and excessive bleeding. On her admission to the hospital at 5:45 P.M., the urine showed a flocculent proteinuria, the hemoglobin was 9.0 Gm., but the clotting time was not prolonged. The blood pressure registered 160/110 and the uterus was rigid and tender. Sedative was administered, also 1,000 c.c. of blood, preceded by magnesium sulfate and glucose solution.

Labor progressed rapidly, aided by artificial rupture of the membranes. There was no placental tissue palpable within reach of the examining finger. A stillborn infant weighing 2,778 grams was delivered at 10:35 P.M. The total blood loss was estimated to have been 900 c.c. Recovery was rapid, the blood pressure returning to normal and the proteinuria disappearing within two days.

The placenta, after fixation, presented the appearance seen in Fig. 10, *A*, in a succession of strips, with numerous localized areas of early "E" acute infarction. Microscopically (Fig. 10, *B*), the appearance was pathognomonic of acute toxemia, namely, narrowing of intervillus spaces, dilatation of villus capillaries, enlargement and crowding of villi, and pyknosis of the chorionic epithelium and karyorrhexis of the capillary endothelium.

It would be difficult indeed to account for the unusually rapid change in the patient's condition by any other mechanism than spasm of the sphincters of the placental veins, followed by very rapid extensive placental infarction, with liberation of thromboplastin, thereby inducing formation of subplacental clots and separation of the placenta.

Dieckmann,[67] in 1936, called attention to the loss of clotting power of the blood in many cases of abruptio placentae and attributed it to the marked decrease in blood fibrinogen. More recently Schneider,[62] Page,[63] Reid,[64] and others have emphasized the serious effects of excess thromboplastin in producing a hemorrhagic tendency through depletion of fibrinogen in the circulation. Fibrin thrombi, formed intravascularly, are capable of producing widespread damage to organs and tissues by plugging of precapillary and capillary vessels, thus producing ischemia, necrosis, and hemorrhage, unless relieved by prompt lysis of the fibrin. These effects are particularly marked in the liver but are present in other organs and tissues.

In pre-eclampsia and eclampsia, placental infarction is relatively less extensive than in severe abruptio. Hence, there is an increased tendency to clotting in the former but a decreased tendency in the latter if depletion of fibrinogen occurs. Separation of the placenta precludes absorption of possible additional breakdown products of placental necrosis, which probably explains why so few patients manifest both abruptio and eclampsia.

TABLE I. TRUE TOXEMIA OF PREGNANCY (APPARENTLY INITIATED BY SPASM OF SPHINCTERS OF PLACENTAL VEINS)

I. Partial Involvement of Veins apparently causes *Localized infarction(s)* and *Subacute toxemia*	*II. Complete Involvement of Veins* apparently causes *Generalized infarction* and *Fulminating toxemia*
1. Mild toxemia, to	1. —
2. Moderate toxemia, to	2. —
3. Severe toxemia, to	3. —
4. Pre-eclampsia, to	4. —
5. Eclampsia	5. Abruptio placentae
Course	*Course*
One to several weeks	Several hours to several days
Eclampsia and abruptio placentae rarely combined	

As previously mentioned, the severity and rapidity of placental vein sphincter spasm and the extent of involvement probably determine the course of the toxemia (Table I).

In *II*, extensive spasm and resulting massive infarction of the placenta cause thromboplastin effect to dominate. Hence, Stages 1, 2, 3, and 4 are bypassed and abruptio placentae occurs.

It is only reasonable to believe that, as placental necrosis progresses, there must be early and late degradation products of nuclear and protein degeneration, some of which may be toxic. Practically all tissue cells possess intracellular enzymes which, upon death of the cells, rapidly break down the nuclear and protein cellular elements, producing endotoxins of potential toxicity. An important part of the problem is to know in what respects placental autolytic products may differ from those of other tissues. It is believed that biochemical methods may make it possible to identify products of placental autolysis and determine their toxicity or effects.

The biochemical products of normal placenta autolyzed in vitro and infarcts from toxic placentas in various stages of previous autolysis in vivo are being studied. It is hoped that blood may be obtained from a uterine vein of a patient with severe pre-eclampsia, eclampsia, or abruptio placentae who, on account of possible resistance to induction of labor, may require delivery by cesarean section, thus affording an opportunity to obtain autolytic products directly from the source in the uterus before such products have passed through the general circulation and have possibly become diminished or altered. Peripheral blood, removed at the same time, should show differences in comparison with uterine blood. This procedure has already been satisfactorily applied in a nontoxic patient requiring cesarean section, the results of which case should serve as a control.

Conclusions

This article is concerned with certain significant anatomical, physiological, and pathological data which seem particularly pertinent to the etiology of eclamptogenic toxemia, setting forth a theory of the genesis of this disease as dictated by these facts and significant phenomena.

The following conclusions seem warranted:

1. There is a specific placental pathology in the form of acute and subacute placental infarction, best demonstrated in formalin-fixed placentas, which is pathognomonic for pre-eclampsia, eclampsia, and abruptio placentae. This fact, first discovered by Young, is pertinent to the etiology of the disease.

2. Areas of placental necrosis in contact with maternal intervillus circulation present possibilities of dissemination of products of placental autolysis, which may be highly toxic to the mother.

3. Placental infarction of the subacute ("C") or acute ("D" and "E") types of infarction is logically the cause and not the effect of toxemia of pregnancy. The paths and interrelationship of the fetal and maternal components of the placental circulation dictate this conclusion.

4. The anatomical basis of placental infarction is found in the presence of smooth-muscle sphincters in the placental veins, first discovered by Spanner.

5. The trigger which excites spasm of few or many of the venous sphincters is logically oxytocin, which through changes in hormone balance in the latter part of pregnancy (lowered progesterone and presence of free estrogen) is apparently released from the inhibition exerted by its hormonal antagonists progesterone and pitocinase. Increase in desoxycorticosteroids late in pregnancy, aided by salt, sensitizes the smooth muscle of vessel walls and probably that of placental vein sphincters to increased reactivity.

6. Spasm of the venous sphincters obstructs exit of fetal blood from the corresponding placental units, causing distention of villus capillaries, enlargement of villi, diminution or obliteration of the intervillus spaces and circulation, resulting in anoxic necrosis of chorionic epithelium, villus stroma, and capillary endothelium.

7. Thromboplastin, abundant in placental tissue, is apparently the first product of chorionic necrosis, which, if infarction is extensive, causes abruptio by subplacental clot formation and occasionally afibrinogenemia with hemorrhagic tendency.

8. It is apparent that there is only one true toxemia of pregnancy—that due to placental infarction and necrosis. It comprises abruptio placentae, eclampsia, and its precursor, pre-eclampsia. Other conditions presently included in the accepted classification of toxemias of pregnancy constitute predisposing causes rather than types of toxemia.

9. It is hoped that biochemical study of normal and toxic placentas and blood now in process may serve to identify the nature and effects of other degradation products of placental necrosis, which are probably more concerned with pre-eclampsia and eclampsia.

A grant-in-aid has made it possible to pursue this line of investigation with the collaboration of Alfred Wilhelmi, Ph.D., Professor of Biochemistry, Emory University School of Medicine, Charles Hoover, Ph.D., Biochemical Research Assistant in the project, and Miss Carolyn Martin, Technician.

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HISTOGENESIS OF PATHOLOGICAL PROCESSES IN PLACENTAS OF METABOLIC DISEASE IN PREGNANCY

I. Toxemia and Hypertension*

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DIECKMANN[5] is of the opinion that "there is now sufficient evidence indicating that the placental tissue, meaning both maternal and fetal, must be given much more consideration with reference to the etiology of pre-eclampsia-eclampsia." Both Dieckmann[5] and Page[16] have reviewed the evidence supporting such a concept. While it appears, at the present time, to offer the most logical approach to an explanation of the mechanism of this disease, studies dealing with the morphological changes in the placenta have yielded a paucity of supporting evidence, much of it inconclusive.

No attempt will be made here to review the literature dealing with the placental changes in toxemic states since this has been well covered by both Dieckmann and Page. The morphological changes described consist, in large part, of an intensification of degenerative vascular processes or of degenerative phenomena in villi, including infarction, seen in normal pregnancy. Accordingly, Harer[9] has concluded that the changes found in the placentas from patients with toxemia of pregnancy are identical with, but occur more frequently and are more extensive than, those found in the placentas from normal pregnant patients.

In order to account for an etiological role of the placenta in pre-eclampsia-eclampsia, the clinical manifestations of the latter have been attributed to (1) toxic or allergic effects of products of placental degeneration, (2) the elaboration of a pressor substance as a result of ischemia of intramuscular (uterine) arteries with a loss of inactivating enzyme activity present in normal pregnancy states, or (3) the increased release of a thromboplastic substance as a consequence of placental ischemia. All of these explanations fail to account adequately for the etiology of factors which may initiate either placental or uterine ischemia; nor do they account for the source of a circulating pressor agent.

A fourth theory holds that this disease is due to altered hormone metabolism. While this might account for the initiation of many of the clinical manifestations of toxemic states, its anatomical source also remains uncertain.

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In a previous study[2] in which the criteria which characterize adult arteriosclerosis were applied, we were unable to obtain evidence to support the concept that vascular lesions are responsible for the degenerative processes observed in the mature placenta of normal pregnancy. On the contrary, the placental vessels were remarkably free of degenerative lesions; in no instance was plaque formation, thrombosis, or occlusion found. Endarteritis could not be demonstrated and the only noteworthy vascular finding was a marked medial hypertrophy of fetal arteries in the placenta and umbilical cord, an effect attributed to maternal hormones and likened to the muscular hypertrophy of uterine arteries in pregnancy.

Furthermore, examination of villi failed to reveal syncytial changes comparable to plaque formation. However, an acellular, fibrinlike periodic acid-Schiff positive material was seen to be deposited in the stroma of villi and supporting trabeculae; eventually this material distended such villi and caused rupture of the attenuated syncytial covering over which it subsequently spread. From such observations it was concluded that "infarction" resulted from a coalescence of many villi so involved. This conclusion appeared to be supported also by the presence of patent vessels and scattered, apparently living, cells in such pseudoinfarcted areas, as well as by the absence of syncytial or vascular alterations resembling arteriosclerosis.

From this initial study it was concluded that although there were no vascular changes of significant degree in normal pregnancy, the action of a pressor substance as has been proposed by Page might lead to degenerative vascular phenomena and possibly to true infarct formation in hypertensive-toxemic states. The present study, therefore, initially dealt with a comparison of the histological changes in placentas of normal and hypertensive-toxemic pregnancies, utilizing methods previously employed. While these studies were generally disappointing from the standpoint of detecting vascular lesions and their complications, certain changes in syncytial buds were detected and quantitated which are offered as a possible anatomical source for altered hormone metabolism in toxemic states, and which may also explain some of the clinical manifestations of this disease.

Materials and Methods

Placentas were collected from 62 pregnancies in which a diagnosis of hypertensive toxemia was made. Only 56 were included in this study, however, 6 being eliminated either because of poor preservation of tissue or because of inadequate history.

Fig. 1.—Umbilical artery, microincineration. There is slight intensification of calcium in areas along the endothelial line. Within the wall calcium appears to be localized in muscle nuclei. Internal elastic lamella (see Fig. 2) fails to show calcification. (Approximately ×100; reduced ⅓.)

Fig. 2.—Umbilical artery, Weigert-Verhoeff stain. This is from the same block as Fig. 1. Note focal intimal thickening, but absence of lipid. The internal elastic lamella is a definitive structure showing focal areas of duplication. (Approximately ×100; reduced ⅓.)

Fig. 3.—Placental arteries, Weigert-Verhoeff stain. Note subnuclear vacuolization in endothelial cells. This represents hydropic degeneration and *is not early atheroma formation.* Such droplets are fat negative and endothelial cells show no significant enlargement. Note also relative thickness of muscular coat in comparison with diameter of lumen. (Approximately ×150; reduced ⅓.)

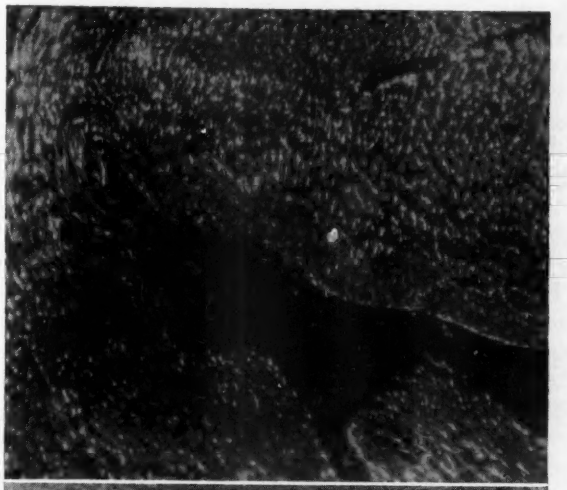

Fig. 1.

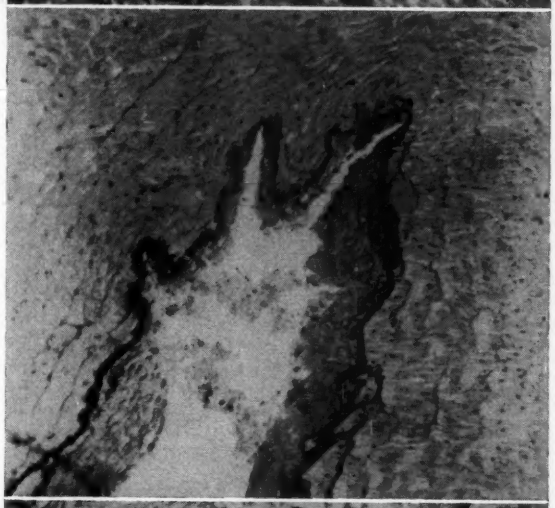

Fig. 2.

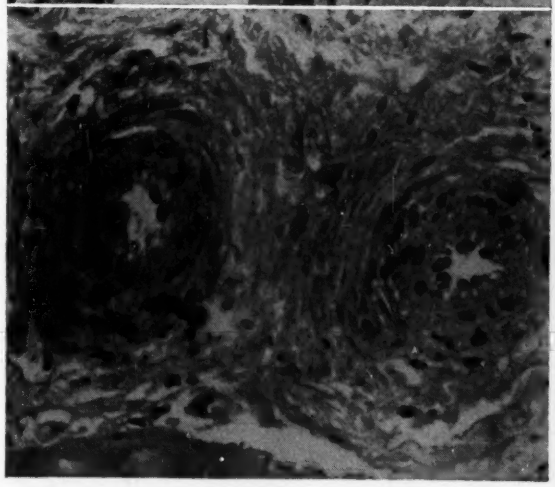

Fig. 3.

Figs. 1-3.—*For legends see opposite page.*

A segment of umbilical cord approximately 1.5 cm. in length and a peripheral wedge of placenta measuring 1.5 by 2.5 cm. were excised from each specimen. These were fixed in alcohol-formalin and processed as previously described. Successive sections of cord and placenta were stained with hematoxylin-eosin, with the Weigert-Verhoeff stain for elastic tissue, with a modified periodic acid-Schiff (PAS) stain for mucopolysaccharide, and with the van Gieson technique for connective tissue and muscle. One section was also microincinerated for dark-field study of mineral distribution.

In the course of study of the material from cases of toxemia it became apparent that there was a striking increase in the number and size of syncytial buds projecting from villi. Accordingly a technique was devised for determining the average number of buds per unit field. A glass disk etched with a square area was inserted into the ocular of a microscope and the number of syncytial buds in 10 random fields of each specimen was counted and an average taken. This technique was carried out in 50 placentas from normal term pregnancies and in 56 from cases of toxemia. The results were then subjected to statistical analysis and are shown in Table I.

The slides were examined initially without benefit of history and after the entire study had been completed a correlation between history and microscopic findings was attempted. The prenatal and postpartum records were then reviewed and the cases grouped according to the criteria established in 1952 by the American Committee on Maternal Welfare. Thus there were 4 groups of cases as follows: (1) mild pre-eclampsia, (2) severe pre-eclampsia, (3) eclampsia, and (4) chronic hypertensive disease with pregnancy.

Results

Umbilical Vessels.—The changes in these vessels in toxemic patients were not qualitatively different from those in normal pregnancy. In general there were more specimens showing a partial or continuous thin layer of intima than in the normal, but its thickness was of a degree comparable to that previously reported. The quantity and distribution of the PAS positive material were also similar to those seen in the normal term placenta and there was no increase in the calcium content of the walls of these vessels as determined by microincineration (Fig. 1).*

The most striking difference consisted of a diffuse increase in the quantity of elastic tissue in the arteries, although the zonal distribution was unchanged. Elastic fibrils were present along the junction of intima and media and between the two strata of muscle. In 3 cases there was a definite well-formed internal elastic lamella (Fig. 2); such an organized structure had not been found in the normal series. No differences were noted in the umbilical veins between normal and toxemic groups; the internal elastic membrane was a well-organized structure even in the normal term placenta.

Placental Vessels.—The placental arterial and venous channels of all sizes were lined by a single layer of endothelium supported by a PAS positive basement membrane. In some instances mild hydropic degeneration of the endothelium was noted, but this was also present in normal placentas. The basement membrane was thicker in the arterial than in the venous system as previously noted. Unlike the umbilical vessels, no elastic tissue was found in either arteries or veins and the wall consisted of only a single, relatively thick layer of muscle (Fig. 3). The ratio of lumen to over-all diameter was essentially the same as in normal pregnancy and there was no increase in mineral deposition in the wall. No evidence of plaque formation or of thrombosis was found.

*All illustrations, with the exception of Fig. 6, are from cases of toxemia.

Supporting Trabeculae.—As in normal pregnancy, some of the supporting trabeculae showed elastic fibrils either immediately beneath the epithelium or beneath the PAS positive basement membrane. In 10 of the cases of toxemia (18 per cent) this elastosis was marked and in 8 cases (15 per cent) it was mild; in 38 cases (67 per cent) no evidence of elastosis was found. This is in contrast to an incidence of 12 per cent with severe and 34 per cent with mild elastotic reactions in controls; 54 per cent of controls also failed to show evidence of elastic tissue.

Chorionic Plate.—This showed the most intense degenerative change, including calcification, of all of the structures which constitute the placenta. While it appeared intensified in the toxemic group, this could not be established on a significant quantative basis because of the already high intensity in normal pregnancy.

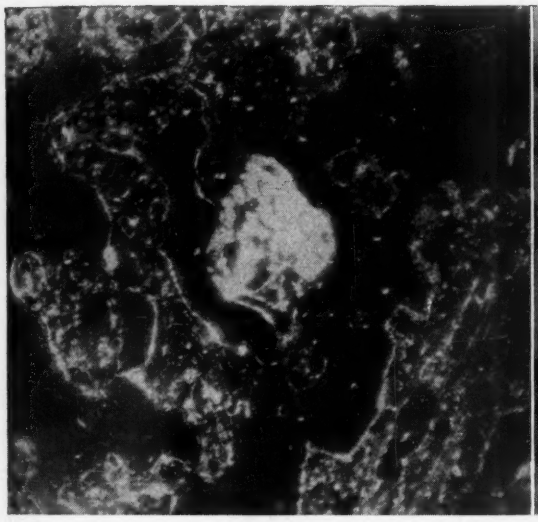

Fig. 4.

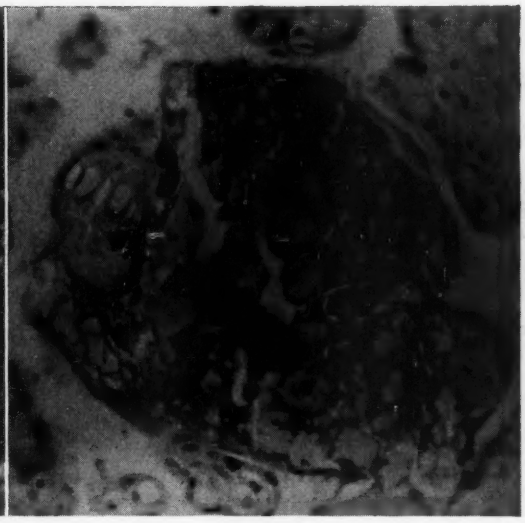

Fig. 5.

Fig. 4.—Chorionic villi, microincineration. In the center there is an intensely calcified villus. Note also distinct calcific lines in other villi corresponding to PAS positive basement membranes of syncytium. (Approximately ×100; reduced ⅙.)

Fig. 5.—Chorionic villi, hematoxylin-eosin stain. Section shows rock formation of villi in the center of the photomicrograph. (Approximately ×150; reduced ⅙.)

Villi.—The size of the villi varied as in the normal group, although there appeared to be a relative increase in the number of smaller ones. Furthermore, the stroma was more frequently fibrous than loose and myxoid as in normal pregnancy. Areas of pseudoinfarction were more numerous and the deposition of PAS positive material more abundant in cases of toxemia. In addition there was a striking increase in the number of villi showing calcification and the latter process was distinctly intensified (Figs. 4 and 5). By the use of an arbitrary grading system of 0 to 3 plus to express intensity of calcification, 10 cases showed 3 plus intensity, 18 cases 2 plus, 20 cases 1 plus, and 8 were without significant calcium deposition. Calcification beyond 1 plus intensity was rarely seen in the villi of normal term placentas.

The most striking alteration, however, was the increase in number and size of the syncytial buds (compare Figs. 6 and 7). Most of these buds showed intact, sharply outlined nuclei, but there were occasional instances of nuclear degeneration including pyknosis and karyorrhexis. The cytoplasm of many buds continued PAS positive cytoplasmic inclusions (Fig. 8) and microincineration showed an increase in calcium deposition which, unlike that in the

normal group, was not limited to the nuclei but included also the cytoplasm. The syncytial layer, in general, rested on an intensely PAS positive basement membrane which frequently showed marked calcium impregnation. As in the normal group, no lesions of the syncytium comparable to plaque formation in arteries were found.

TABLE I. COMPARISON OF NUMBER OF SYNCYTIAL BUDS IN THE PLACENTAS OF NORMAL AND TOXEMIC PATIENTS

GROUP	NO. OF CASES	AVERAGE NO. OF SYNCYTICAL BUDS PER UNIT FIELD	RANGE OF VARIATION	STANDARD DEVIATION	STANDARD ERROR
Normal	50	6.4	2.0-11.3	±2.1	±0.94
Toxemic	56	14.9	5.0-24.7	±5.1	±2.20

The data in Table I show the results of syncytial bud counts in the two groups. The average number per unit field was over twice as great in toxemic as in normal patients. Although the column giving range of variation in individual counts shows some overlap, there were only 11 of the 56 cases of toxemia with counts below the highest single count in the normal group, and only 2 of the 56 cases of toxemia gave counts below the normal average. The columns showing standard deviation and standard error show that this difference in average count is a highly significant one, approaching a 95 per cent confidence limit.

According to the criteria of the American Committee on Maternal Welfare our 56 cases were classified as follows: 36 cases of mild pre-eclampsia, 13 of severe pre-eclampsia, 2 of eclampsia, and 5 of hypertensive vascular disease. There was no distinct correlation between the intensity of the placental changes and the severity of the disease or the duration of symptoms, although, in general, the placentas with the most intense calcification and highest syncytial bud counts were in cases with severe symptoms. There were, however, a number of instances of mild disease and marked placental changes, and, conversely, there were a few cases with severe disease and relatively mild alterations in the placenta. Furthermore, no distinction could be made between true eclampsia and chronic hypertensive disease with pregnancy.

Comment

Most concepts of the etiology of toxemias which conceive of the placenta as playing an important causal role attribute this to degenerative changes, the products of which initiate a series of events leading to the characteristic symptomatology of the disease. Page believes that there are a number of extrinsic and intrinsic factors which may impair the nutrition of the placenta rather acutely by decreasing the maternal blood supply; in response to this the placenta in some way releases some chemical substances which cause toxemia in susceptible subjects. It is not clear whether in this view the usually described degenerative processes are essential to the release of such substances or are merely incidental to the decrease in maternal blood supply.

Essential to either of the foregoing concepts is a demonstration of vascular lesions to account for placental ischemia. Heretofore most studies dealing with histological changes in the placentas from cases of toxemia at best indicate only some degree of intensification of degenerative processes commonly seen in placentas of normal pregnancy. While some investigators have described lesions resembling arteriosclerosis of both maternal and fetal vessels,

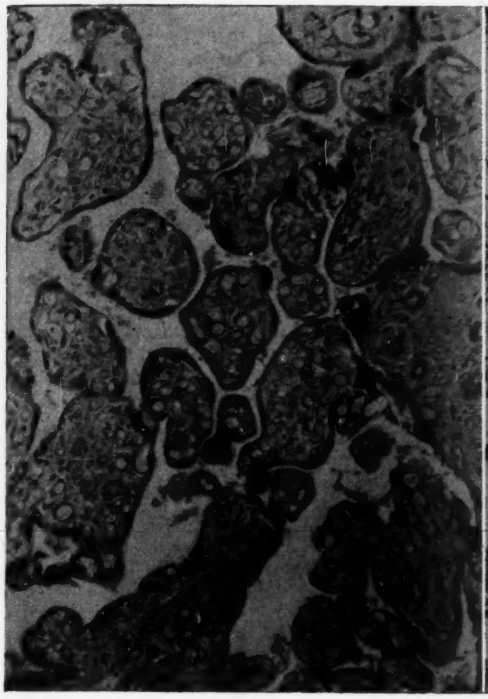

Fig. 6.

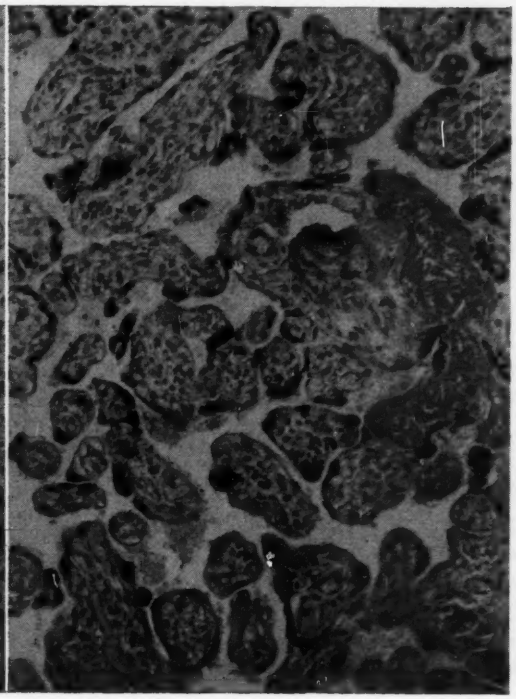

Fig. 7.

Fig. 6.—Chorionic villi, hematoxylin-eosin stain. Section is from a term placenta of normal pregnancy. Note number and distribution of rounded black masses representing syncytial buds. (Approximately ×100; reduced ⅕.)

Fig. 7.—Chorionic villi, hematoxylin-eosin stain. Section is from a term placenta of a case of toxemia for comparison with Fig. 6. Note diminution in size of villi and marked increase in numbers of syncytial buds. (Approximately ×100; reduced ⅕.)

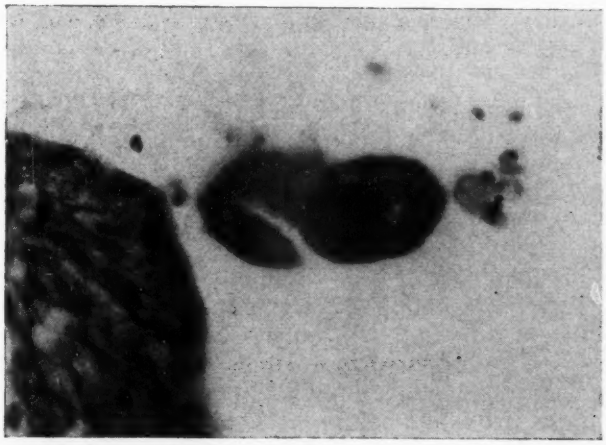

Fig. 8.—Syncytial bud, periodic acid-Schiff stain. Black mass in center represents PAS positive cytoplasmic inclusion, and is distinct from nuclei. (Approximately ×450.)

Page states that only the larger fetal vessels, in surprising contrast to those of the fetus itself, very often show atheromatous changes. We have been unable to substantiate this observation either in normal pregnancy or in toxemia. Page further states that atheromatous changes are not common in

maternal vessels unless hypertension is present. Again, our material fails to show such lesions either in the placentas of normal pregnancy or in those of toxemia.

The only noteworthy findings in vessels in the present study were those in the umbilical arteries which showed an increase in elastic elements. In several cases an organized internal elastic lamella was found, in striking contrast to the 50 normal term placentas studied where such a structure was never encountered. This may represent a response to increased intravascular tension, although placental vessels appear to be peculiarly protected against such effects. In contrast to arteries in other locations, placental vessels other than the umbilical artery and veins have a relatively thick muscular coat and lack any semblance of elastic elements. Rarely are thrombi found in either umbilical or placental vessels and these are not associated with thickening of the intima (Fig. 9).

In this regard the microscopic changes in the minute vessels of the maternal decidua as described by Zeek and Assali[27] deserve special consideration. While we have been unable to corroborate these observations, it should be pointed out that no special techniques have been utilized here especially designed to demonstrate such lesions, as employed by these investigators. They stated that the lesions were seen only rarely in normal cases, but were present in at least three-fourths of the placentas from cases of toxemia; they consisted of acute atheromatous changes, frequently with complete vascular occlusion. On the other hand, the more general studies of Karsner[13] as well as those of Masson[15] and of Koletzky[14] have not shown an atheromatous component in the development of acute inflammatory vasculitis. The studies of Masson and of Koletzky are particularly pertinent, since they deal with the importance of electrolyte imbalances in the development of such lesions.

In the light of the foregoing observations, the lesions described by Zeek and Assali, if valid, may represent a complication rather than a causal factor of eclampsia. However, we have observed rounded masses of decidual cells with a central capillary or area of hemorrhage, surrounded by fibrous tissue or fibrinoid which mimic blood vessels (Fig. 10). These are frequently in areas of necrosis with infiltration of leukocytes and even with calcification. Such masses have been observed in which the large decidual cells resembling lipoid-laden macrophages form a solid central cord simulating an occluded vessel. Special stains for distinguishing muscle from fibrous tissue have, in all instances, made possible the elimination of these structures as vessels.

There appears to be common agreement that there is an acceleration of degenerative changes in chorionic villi in toxemic states. Wislocki and Dempsey[24, 25] believe that there is histochemical and cytological evidence of advanced aging of the syncytium, and that the essential lesion in pre-eclampsia is a premature aging of the villi. Intensification of degenerative processes in villi in the present study consisted of an increased deposition of PAS positive, fibrinlike material in the stroma and rather marked calcification. As pointed out previously, these probably represent connective tissue responses to maternal hormones. Similar processes were also seen in the chorionic plate, and in supporting trabeculae. However, the latter failed to show evidence of increased formation of elastic tissue; if anything, the intensity of the latter process was less than in the normal term placenta.

As regards true infarct formation, its increased frequency and severity in toxemia as reported by Bartholomew and Colvin[1] and by Falkiner[7] are not supported by the studies of Traut and Kuder.[21] If the observations of Bar-

tholomew and Colvin and of Falkiner are valid, they serve only to emphasize again an increased severity of degenerative processes in toxemia which are found in somewhat milder form in normal pregnancy.

Evidence for intensification of degeneration of syncytium other than that resulting from pressure of increased fibrinoid deposition was, however, lacking in toxemic placentas. In contrast to the observations of Tenney[20] of an increased severity of syncytial degeneration in toxemia, we have noted an

Fig. 9.

Fig. 10.

Fig. 9.—Large placental artery, hematoxylin-eosin stain. In the center there is a mass of thrombus attached to the endothelium (in polypoid fashion) at one point. Note absence of any endothelial or intimal lesion. (Approximately ×100; reduced ⅕.)

Fig. 10.—Placental capillary, Weigert-Verhoeff stain. This is presented to illustrate pseudoatheroma formation. The capillary lumen courses across the center of the photomicrograph. On either side of the lumen there are bands of decidual cells of varying thickness which resemble lipid macrophages. At *A* there is a band of acellular fibrinoid resembling necrotic vessel wall, and beneath this a second layer of decidual cells. At *B* there is a cluster of small inflammatory cells. (Approximately ×250; reduced ⅕.)

increase in the size and number of syncytial buds, the latter supported by quantitative data. According to Stander,[19] there are many more syncytial buds at 4 months' normal gestation than at 8 months; presumably in normal pregnancy with advancing age of the placenta there is a progressive degeneration of such buds and a loss of reproductive capacity of the syncytium. The surprising paucity of information in the literature on these structures emphasizes the importance of further study in regard to the capacity of the syncytium to form buds as well as factors which control this process.

While it cannot be determined from this study what position the process of syncytial bud hypertrophy and hyperplasia holds in the chain of causal events leading to the clinical manifestations of toxemia, it may nevertheless play an important role, particularly in regard to the placental elaboration of hormones and the resulting peripheral effects. Accumulating data indicate a placental elaboration of steroid hormones,[6, 12, 22, 26] including sex and adrenal cortical hormones[8, 11] as well as gonadotropins.[18] In addition Hechter and associates[10] have shown that progesterone may be converted to an 11-oxysteroid with cortical hormone activity. There remains some question as to whether or not the level of adrenal cortical hormones is increased in toxemic states, although recent reports[3, 4, 23] appear to support such a conclusion. The role of excessive adrenal cortical hormone in salt retention edema[5, 16] and hypertension[17] is well known.

Evidence is therefore accumulating which supports the concept that the clinical manifestations of toxemia may, in large part, be attributed to altered steroid hormone metabolism. The present observations on syncytial changes indicate a possible additional source of such steroid hormones, although the intensity of these alterations does not correspond accurately with the severity of clinical manifestations. Such attempts at correlation generally suffer from the fact that it is not possible to evaluate compensatory phenomena which may ameliorate symptoms.

From our observations it appears that most of the lesions in the placenta heretofore described are of a secondary character similar to those observed in liver, kidney, and other organs. On the other hand, the changes in activity of the syncytial buds appear more closely related causally to the basic disease, although the ultimate etiology may reside in factors which control the formation and activity of the syncytium. Experiments are planned to test this thesis.

Summary

This report consists of a study of the histological changes in the placentas of 56 cases of toxemia of pregnancy. Many of the changes consisted only of an intensification of pathological processes previously described in the normal placenta. Included in the latter category are increase in the formation of elastic tissue in the umbilical arteries, calcification of the chorionic plate and villi, and deposition of fibrinoid in villi. No noteworthy vascular lesions were encountered, although rare thrombi were found in large placental arteries; the latter could not be attributed to intimal pathology.

The most striking change consisted of a significant increase in the number and size of syncytial buds and the appearance of PAS positive concretions in

the cytoplasm of many of the buds. The significance of these findings is discussed in so far as they may be related to the altered steroid hormone metabolism which appears to account for much of the symptomatology of toxemia.

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HISTOGENESIS OF PATHOLOGICAL PROCESSES IN PLACENTAS OF METABOLIC DISEASE IN PREGNANCY

II. The Diabetic State*

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DESPITE the commonly accepted concept that the human placenta is an aging organ with a life span telescoped into a nine months' period, and that an essential part of this aging process involves degenerative lesions of vessels resembling adult arteriosclerosis, previous studies by us[5] have failed to disclose significant vascular lesions in the normal term placenta. Nor have we[4] been able to find noteworthy pathological changes in placental vessels in cases of toxemia or hypertension of pregnancy. On the contrary, the placental vessels, with the possible exception of the umbilical artery, appear to be peculiarly protected from possible adverse effects of maternal blood pressure.

Since vascular complications appear to be common in diabetic individuals, it was thought that a study of the placenta in this disease might prove fruitful in this regard. Surprisingly, a preliminary survey of the literature failed to disclose anything of note with respect to diabetes, although, as previously pointed out, there are many reports dealing with vascular lesions in the normal placenta and in toxemia and hypertension in pregnancy. Furthermore, personal communication with Novak,[18] Dieckmann,[6] Hellman,[10] Reis,[22] Potter,[20] White,[29] and others expressed the opinion that nothing distinctive about the placenta in diabetes has been reported, although studies are in progress in several institutions.

In previous investigations we have employed histochemical techniques which might prove useful in such a study. One of these in particular, the periodic acid-Schiff reaction, has been extensively used in the characterization of the vascular lesions of the retina and renal glomerulus in diabetes. It was therefore anticipated that a careful comparison of the placentas of diabetic patients with those examined in previous studies might yield information regarding vascular changes in the placenta in diabetic states.

A second anticipated aspect of the problem concerns changes in syncytial buds. In the study dealing with placentas in toxemic-hypertensive states,[4] a striking hyperplasia of syncytial buds was discovered, and consideration was given to the possibility that these structures might play an important role in

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the altered steroid hormone metabolism of that disease. Since it is well known that steroid hormones may also play an important role in carbohydrate metabolism, a comparison of syncytial bud changes in toxemic and diabetic patients was also carried out.

Fig. 1. Fig. 2.

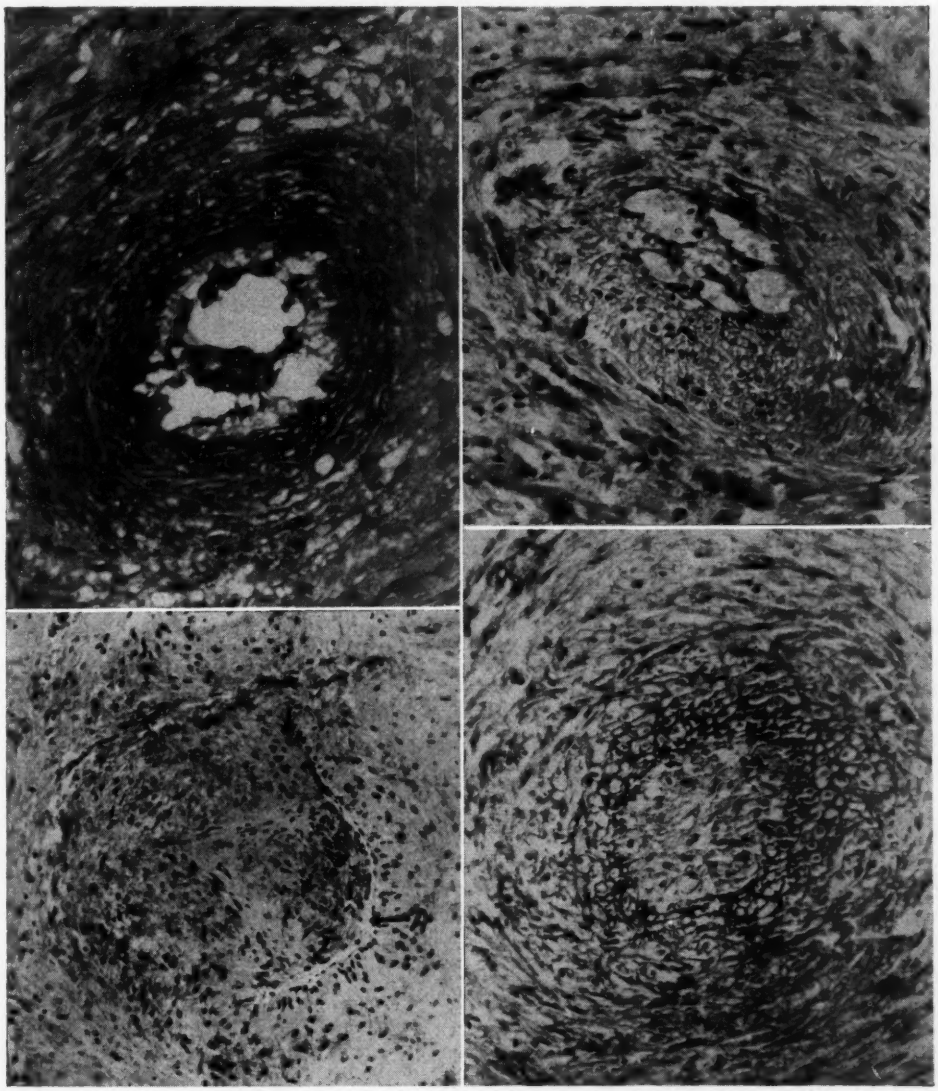

Fig. 3. Fig. 4.

Fig. 1.—Placental artery, periodic acid-Schiff stain. Section shows initial marked swelling of the lining endothelium. The lumen contains a hyaline (PAS positive) concretion. (Approximately ×100; reduced ⅓.)

Fig. 2.—Placental artery, periodic acid-Schiff stain. Section shows bridging of the lumen by proliferating endothelial cells so that lumen consists of a net of 5 separate channels. There is no hemosiderosis or other evidence of previous thrombosis, so that this cannot be construed as recanalization of a thrombus. (Approximately ×100; reduced ⅓.)

Fig. 3.—Placental artery, Weigert-Verhoeff stain. This shows a lesion similar to that seen in the umbilical artery (Fig. 1) and shows progression to marked narrowing of lumen which is the slit at *A*. (Approximately ×100; reduced ⅓.)

Fig. 4.—Placental artery, periodic acid-Schiff stain. Section shows progression of the endarteritis to complete obliteration of the lumen. Note also the network of PAS positive fibrils coursing between endothelial cells. (Approximately ×100; reduced ⅓.)

Material and Methods

The placentas of 20 diabetic patients are included in this study. These were compared with the 50 normal term placentas and the 56 specimens from cases of toxemia and hypertension previously described.

An in previous studies, a segment of umbilical cord and a peripheral wedge of placenta measuring 1.5 by 2.5 cm. were excised. These were fixed in alcohol-formalin and successive sections of cord and placenta stained with hematoxylin-eosin, the Weigert-Verhoeff stain, a modified periodic acid-Schiff (PAS) stain, and with the van Gieson technique. A final section was microincinerated. This series of preparations permitted a study of the distribution of elastic, muscle, and connective-tissue fibers as well as of mucopolysaccharide and minerals.

The determination of the average number of syncytial buds per unit field was carried out as previously described,[4] and the values obtained were subjected to a statistical analysis as shown in Table I.

The history of each case was reviewed for the purpose of determining duration and severity of the diabetic state according to the criteria of Jones,[14] the outcome of the pregnancy as regards birth weight and infant survival, and the evidence of pelvic calcification.

Results

Umbilical Vessels.—In general, the umbilical arteries and vein appeared the same as in previous studies of normal and toxemic cases. In 2 instances, however, an intact definitive internal elastic lamella was found similar to that seen in several toxemic patients, but not in normal pregnant women. There was also a single case showing an eccentrically positioned mound of proliferating endothelium capped by a layer of fibrin and degenerating cells. Fine PAS fibrils were scattered between endothelial cells, but no inflammatory reaction was seen. Microincinerated sections showed no increase in mineral deposition.

Placental Vessels.—The placental veins, as in previous studies, showed no significant change. However, the placental arteries showed a rather striking endarteritis. While this was present in some degree in 17 of the 20 placentas, it was marked in only 9 cases. The lesion involved arteries of all sizes, and in one case extended into precapillary arterioles (Fig. 5).

Various stages of the lesion were noted. It appeared to begin as a swelling of the lining endothelium (Fig. 1) accompanied by reduplications of the PAS positive basement membrane. As the endothelium proliferated into the lumen, successive bands of mucopolysaccharide were laid down (Fig. 4). In some instances bridges of endothelium formed across the lumen dividing it into several channels (Fig. 2). There was no significant increase in mineral deposition in these lesions, nor was there any notable change in the media which showed the hypertrophy previously described.

Progressive narrowing of the lumen by this endarteritic process was common, and in one instance obliteration of the channel was noted (Figs. 3 and 4). Thrombus formation was found in 4 cases.

Fig. 5.—Chorionic villus, periodic acid-Schiff stain. Many small precapillary arterioles show swelling and proliferation of endothelial cells (*A*). At *B* there is a dilated capillary suggestive of a capillary aneurysm. (Approximately ×250; reduced ⅙.)

Fig. 6.—Chorionic villus, microincineration. Section is from the same block as that shown in Fig. 5. Note calcium line of basement membrane of syncytium which also extends around vessels showing the precapillary endarteriolitis. (Approximately ×200; reduced ⅙.)

Fig. 7.—Chorionic villus, periodic acid-Schiff stain. This is a true infarct. Note loss of nuclei of the syncytial layer and the marked pyknosis of nuclei and degeneration of connective tissue cells of the stroma. (Approximately ×150; reduced ⅙.)

Fig. 5.

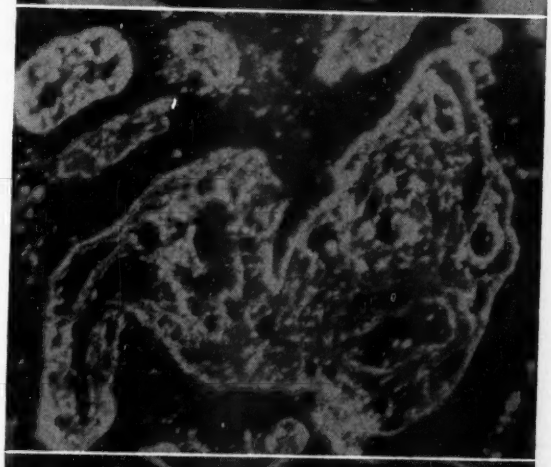

Fig. 6.

Fig. 7.

Figs. 5-7.—*For legends see opposite page.*

While we were unable to find microaneurysms of capillaries as described in the retinas and glomeruli of diabetics, there appeared to be marked dilatation of single capillaries in some villi in which other capillaries were small. However, the basement membrane of the dilated channel appeared no different from those of the smaller vessels.

Chorionic Plate.—The intensity of fibrinoid deposition and calcification was generally more intense than that seen in normal pregnancy and was comparable to that observed in the toxemic-hypertensive group. As previously noted, the chorionic plate showed the most intense degenerative changes of all of the structures of the placenta.

Villi.—In most instances the changes in villi were also comparable to those seen in hypertensive-toxemic cases. There was increased calcification of basement membrane (Fig. 6), syncytial buds and stroma of villi. As in the toxemic-hypertensive group, there was an increase in the number of villi showing massive mineralization. In addition there was an increased fibrinoid deposition and intensification of pseudoinfarct formation of a degree comparable to that seen in cases of toxemia and hypertension. Many villi and supporting trabeculae showed arborization of PAS positive fibrils forming networks of this material; this was considerably more marked than in the normal group or the hypertensive-toxemic group.

True infarct formation was found in 5 cases (25 per cent), and thus appeared to be more common than that observed in the toxemic-hypertensive group. In all instances these infarcts were present in cases showing severe vascular lesions, and, in several, vascular thrombi were found. These infarcts were distinctly different from the pseudoinfarcts previously described. Whereas in the latter the fibrinoid was strongly PAS positive, the true infarcts lost this affinity and instead took the green counterstain. There was marked pyknosis and degeneration of nuclei of stromal cells of villi, and the overlying syncytium was also necrotic. Furthermore, viable capillaries could not be found in infarcted areas (Fig. 7).

TABLE I. COMPARISON OF SYNCYTIAL BUD COUNTS

GROUP	NO. OF CASES	AVERAGE NO. SYNCYTIAL BUDS PER UNIT FIELD	RANGE OF VARIATION	STANDARD DEVIATION	STANDARD ERROR
Normal	50	6.4	2.0-11.3	±2.1	± .94
Toxemic-hypertensive	56	14.9	5.0-24.7	±5.1	±2.2
Diabetic	20	17.2	12.2 (2.5*)-25.9	±4.8	±1.1

*This was the single low count in this series and is included in the calculation of the average.

The changes in syncytial buds were comparable to those seen in the hypertensive-toxemic group. The buds were generally larger and more numerous and the intracytoplasmic PAS positive inclusions previously described were occasionally found here also. As shown in Table I, the average count in the diabetic group was even higher than in the toxemic-hypertensive cases, and almost three times as high as in the normal group. Only one count was lower than the highest count found in normal pregnancy, and we were unable to explain this single low value. It is doubtful that the difference between the diabetic and hypertensive-toxemic groups is a significant one, but the difference between the diabetic and normal groups is again in the range of the 95 per cent confidence limit.

Correlation With Clinical Findings.—Attempts at correlation of the intensity of the placental changes with severity of maternal disease were unsuccessful. Although information as to the duration of the diabetes was present

in all records, these did not always appear to be reliable. Not all patients had eye ground changes recorded by an ophthalmologist. In only 13 cases was there a note regarding pelvic calcification, and in all it was recorded as negative. Insulin requirement could not be used because different physicians utilized different methods of treatment. Correlation with the number of episodes of ketosis (based on history) was also poor.

The most reliable item for correlation appeared to be fetal survival. In 14 of the 20 cases a living baby was born, but 3 of these died shortly after birth. Of the 9 placentas which showed severe lesions, 4 were associated with the 6 stillbirths, 2 with the 3 infants born alive who died shortly after birth, and 3 with infants who have survived. While there is, therefore, an imperfect correlation, it appears that, in general, the severest placental changes were found in the cases in which the fetus did not survive.

Comment

In common with the hypertensive-toxemic group, the placentas of diabetic mothers showed the occasional formation of a definitive internal elastic membrane of the umbilical arteries, intensified fibrinoid degeneration and calcification of the chorionic plate and villi, increased syncytial bud counts, and occasional syncytial buds containing PAS positive intracytoplasmic masses.

Unlike those of either the normal or hypertensive-toxemic groups, the placentas of diabetic women in about one-third of the cases showed marked endarteritic lesions of vessels which may progress to vascular obliteration or thrombosis and true infarct formation. Milder degrees of these vascular changes were seen in other cases, although they would probably have gone unrecognized were not attention drawn to this problem by the cases showing severe lesions. In 3 of the 20 cases no vascular alterations could be detected.

The frequent occurrence of degenerative vascular lesions in diabetes is now well recognized. Two forms are generally described, (1) an intensification of processes of atherosclerosis, and (2) the development of specific retinal and glomerular lesions. As pointed out in a recent review by one of us[3] the validity of the first of these is in doubt, particularly since Muller[17] has shown that in the patient with controlled diabetes the blood cholesterol is usually normal. As regards those lesions which appear to be specific for diabetes, it is pertinent that Friedenwald[7] has remarked that "other organs have as yet not been adequately explored to disclose the full extent of this vascular disease." Warren and LeCompte[27] believe that faulty mucopolysaccharide metabolism may constitute an important part of the diabetic process, and Jacobs[12] has shown that the levels of bound glucose-amine of serum mucoid parallels the glucose levels. In keeping with this idea McManus,[16] Koss,[15] Friedenwald,[7] and others have emphasized the appearance of a PAS positive mucopolysaccharide in the walls of the specific vascular lesions of diabetes. In addition, Ballantine and Lowenstein[1] have described an initial proliferation and swelling of the endothelium of retinal vessels with subsequent thrombosis which are, in some respects, similar to the lesions which we have observed in placental arteries.

While we have previously emphasized the absence of vascular lesions in the normal term placenta and in the cases of the hypertensive-toxemic type, there are diseases which may produce endarteritic changes in vessels. Such lesions are found in syphilis. All of our cases showed negative serological tests for syphilis, however, and none of the placentas included in this report showed evidence of an increase in stroma or of an inflammatory reaction characteristic

of syphilis. Furthermore, whereas in syphilis the villi become larger, in diabetes as in toxemia they tend to be smaller and perhaps more numerous. Nor did any of the diabetic patients show evidence of erythroblastosis, the placental changes of which have in some respects been compared with those of syphilis.

Hellman[11] has stated that fetal death may not cause placental death, in which case a disuse endarteritis of the vessels of the villi may occur. While it is possible that some of our cases might be explained on this basis, it should also be pointed out that there were 5 instances of live births in this group of diabetic women in which the placentas showed severe lesions. Furthermore, the intensified laying down of PAS positive fibers in these lesions appears to relate them specifically to diabetes. One additional case which was discovered after this study was completed is worthy of mention in this connection. In the course of routine examination of the placenta of a stillbirth at 8 months we noted endarteritic lesions similar to those herein described. Since the attending physician stated that there was no clinical evidence of diabetes, a glucose tolerance test was carried out on the mother. This showed a fall to hypoglycemic levels following the initial rise. Somogyi[26] has observed many cases with similar curves in which clinically manifest diabetes subsequently develops, and, indeed, on further review of records of the 20 cases included in this report, several examples of this phenomenon were found.

It appears, therefore, that not only may there be no correlation between the intensity of the placental vascular lesion and the severity of the diabetes, but the placental lesion may develop even in the prediabetic state. Further study is, however, necessary before the validity of such a conclusion can be established.

In recent years there have been attempts[2, 23] to reproduce experimentally the renal and glomerular lesions of diabetes. Interestingly, these have centered about steroid hormones, based upon the known effects of these hormones on carbohydrate metabolism. In a previous report we[4] have mentioned the relation of certain of the placental changes which now appear to be common to toxemia and diabetes to mineral corticoid metabolism, and have reviewed the evidence to support such a concept. Particularly important are investigations which demonstrate the ability of the placenta to synthesize and secrete such hormones.

Gey, Jones, and Hellman,[9] and Jones, Gey, and Gey[13] have demonstrated by tissue culture techniques the active synthesis of chorionic gonadotropins by trophoblasts. Since their observations, along with those of Friedheim[8] and Sengupta,[25] indicate that the cytotrophoblast rather than the syncytium survives in culture media, it has been concluded that the cytotrophoblast is the source of this hormone. The Langhans cells (cytotrophoblast of the chorionic villi) are capable of division by mitotic activity and by cytomorphosis give rise to the trophoblastic syncytium, but according to Wislocki, Dempsey, and Fawcett[31] they contain no fats or ketosteroids.

By contrast, it is probable that the syncytium is capable of undergoing only a limited degree of independent growth by amitotic division of its nuclei. However, they contain abundant birefringent, sudanophilic lipid droplets throughout gestation. Wislocki and Bennett[30] have shown that these droplets are acetone soluble, react with phenylhydrazine, and give a positive Schiff reaction. Wislocki, Dempsey, and Fawcett have, therefore, concluded that the syncytium is very probably the site of origin of the placental steroid hormones.

Certain of the changes in the syncytium which we have observed in toxemia and in diabetes are therefore consistent with an excessive output of steroid hormones by the placenta. The question arises, however, as to whether a dissociation of mineral corticoid and glucocorticoid effects can occur or the two are essentially inseparable. If the latter is true, a frequent association of diabetes and toxemia would be anticipated. The occurrence of such an association with significant frequency has been considered, and is in dispute.[19, 21, 28] The possibility, however, of no absolute dissociation of mineral and glucocorticoid effects, but rather a dominance of one or the other should also be considered. The observations of Russi, Blumenthal, and Gray[24] on the clinically manifest effects of adenomatous hyperplasia of the adrenal cortex tend to support such a view.

Our observations on the changes in the placenta in toxemic and in diabetic states serve to emphasize the need for further study of the structure and function of the syncytium. As we have previously pointed out, this must include the investigation of factors which control the formation and activities of these cells.

Summary

This report consists of a study of the histological changes in the placentas of 20 cases of pregnancy in diabetic women. Many of the changes consisted only of an intensification of pathological processes previously described in the placentas of normal pregnant women and of pregnant women with toxemia or hypertension. These include increased formation of elastic tissue in the umbilical arteries, calcification of chorionic plate and villi, and fibrinoid deposition in villi.

The diabetic group also showed changes in the syncytial buds and increased syncytial bud counts comparable to those found in the hypertensive-toxemic group. The significance of these changes as related to the importance of steroid hormone metabolism in both disease groups is discussed.

An endarteritis of placental vessels in diabetic mothers has been described which appears not to have been reported heretofore. The resemblance of these lesions to other vascular changes specifically associated with the diabetic state has been pointed out, and evidence for such a specificity of this endarteritis presented.

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THE DIFFERENTIATION OF A SPECIAL FORM OF TROPHOBLAST IN THE HUMAN PLACENTA

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ALTHOUGH much attention has been directed toward various histochemical features of the placenta of various mammalian species, relatively little attention has been given to the nature of the isolated islands of cells in the basal plate and septa of the placenta which were described by Wislocki[8] in the human placenta at term.

In this report Wislocki clearly demonstrated the fetal origin of numerous cells embedded in sheets of fibrin in the basal plate and septa of the placenta, which constitute a persistent trophoblastic shell in the full-term placenta. He found these persistent trophoblasts were strongly basophilic, had periodic acid-Schiff positive (saliva insoluble) stippling (suggestive of chorionic gonadotropin), many mitochondria (phospholipids), no neutral fat, variable amounts of glycogen, and no acid or alkaline phosphatase. He felt these persisting viable cells in the basal plate could be responsible for the continuing production of chorionic gonadotropin.

In the course of a general study of the varying histochemical and histological features of the human placenta during the course of pregnancy we collected a series of placentas varying in age from 3.5 weeks to term. By study of appropriately fixed and stained material from these sources we were able not only to agree with the findings of Wislocki but to furnish additional means of identifying a type of trophoblast distinct from either the typical cellular or syncytial trophoblast, and from the neighboring maternal decidual cells.

Materials and Methods

In all, 14 placentas were obtained, fresh from the delivery room, representing placental ages of 3.5, 5.6, 7.5, 9, 10, 16, 22, and 27 weeks, and full term. The ages of the placentas were compiled from the estimated times of conception. Appropriate segments from each placenta were fixed in 10 per cent formalin, picroacetoformol, 4 per cent basic lead acetate, 5 per cent trichloracetic acid, saturated aqueous corrosive mercuric chloride, and 50 per cent alcohol. After fixation all material was routinely dehydrated in alcohol, cleared in xylene, embedded in paraffin, and cut at 5 μ.

Routine stains used were azure II-eosin, Regaud's hematoxylin and eosin, Masson trichome, and Mallory azan. Taft's methyl green-pyronin stain was

*Most of this study was done while Dr. Beber was a C. W. M. Poynter Fellow in Anatomy at the University of Nebraska.

used for detection of nucleic acids, ribose nucleic acid (RNA) and desoxyribose nucleic acid (DNA). Metachromasia was determined by using 0.5 per cent toluidine blue. Distribution of thiol groups was studied by using Bennett's sulfhydryl reagent. In our hands, using the Taft stain, the specificity of pyronin for RNA was uncertain, possibly because we used too highly polymerized dye, as reported by Monne and Harde.[4] The thiol reagent seemed quite specific as Bennett[1] stated, but color intensity in our material was frequently so slight as to make evaluation difficult, but with prolonged staining periods some visual estimation could be made.

Observations

Groups of cells such as those described by Wislocki were seen in our material at all developmental stages. We found them present not only in the persistent trophoblastic shell of the basal plate of the placenta and along the placental septa but to some extent throughout the placenta, particularly associated with the Langhans layer of degenerate villi and islands of typical cytotrophoblast in placentas of earlier stages, which had become separated from cell columns. We have always found such groups of cells partially or completely embedded in a fibrinoid, hyaline-like matrix which increases in amount with aging of the placenta, which is correlated with the decrease in the amount of thromboplastin present. This material then isolates these cells from both maternal blood and tissues and also from other chorionic elements. Fig. 1.

During the first trimester of pregnancy when typical cytotrophoblast is present and groups of cells are becoming separated from it by deposition of fibrinoid, transitional stages were found between typical cytotrophoblasts and this type of trophoblast which has distinctly different characteristics. Both nuclei and cytoplasm increased in amount, the cytoplasm to greater extent, at least in part due to addition of fluid so that, as cell volume increased, it changed from the regular oval or spherical to an irregular streaming shape caused by this increased fluidity of the cytoplasm. The cell membranes became less distinct and often cytoplasmic bridges seemed to connect adjacent cells (Figs. 1, 2, and 3). Often this proceeded to the point of formation of semisyncytial multinucleated masses (Fig. 2). Nuclear alterations consisted of the enlargement of the prominent nucleoli and an increased deposition of chromatin at the nuclear membrane (Fig. 2). During early stages, however, little DNA could be demonstrated with Taft's methyl green-pyronin stain, but this increased in later stages of pregnancy. The prominent nucleoli and the cytoplasm became increasingly pyronin positive (probably RNA) as pregnancy advanced, just opposite to that seen in the syncytium while typical cytotrophoblasts remained chromophobic. With routin azure II-eosin staining the special trophoblastic elements demonstrated increasing basophilia and a peripheral zone of neutrophilia or basophilia. In placentas of the third trimester, Mallory azan stain revealed a perinuclear zone of purple or violet color and a peripheral zone of red color. But on the other hand the syncytium in the third trimester was weakly acidophilic. Fig. 3.

With the use of Bennett's sulfhydryl technique, highly refractile reddish granules were seen in both cytoplasm and neuclei of these trophoblastic cells. The granules were infrequent early in pregnancy but became progressively more numerous as pregnancy advanced. Thiol groups were also demonstrated to slight degree in both syncytium and cytotrophoblast.

Following fixation in either 4 per cent basic lead acetate or 5 per cent trichloracetic acid, sections were stained with toluidine blue to determine the distribution of metachromasia. Definite metachromatic granules or fibrils (possibly indicative of mucoprotein such as chorionic gonadotropin) were found

in these cells until the third trimester after basic lead acetate fixation (Fig. 1). During the last trimester the metachromasia gradually disappeared, leaving the cytoplasm either basophilic or chromophobic. The tissue retained its

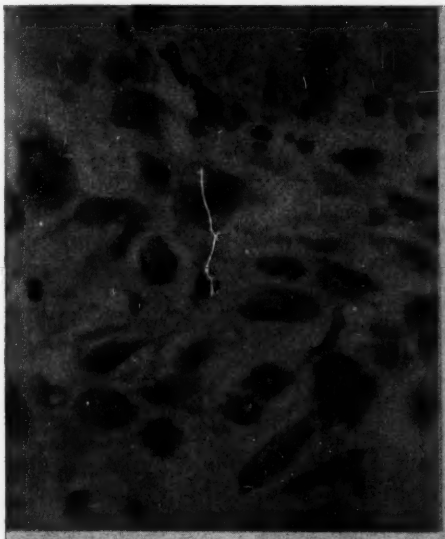
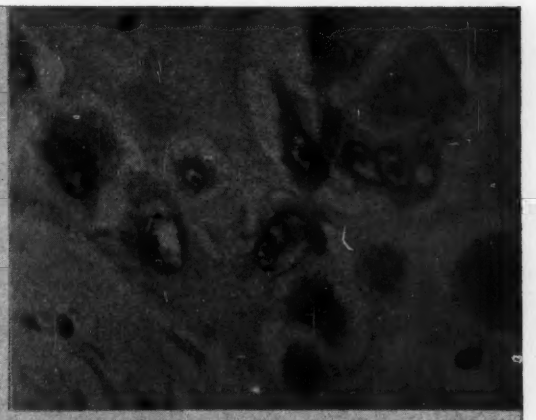


Fig. 1.



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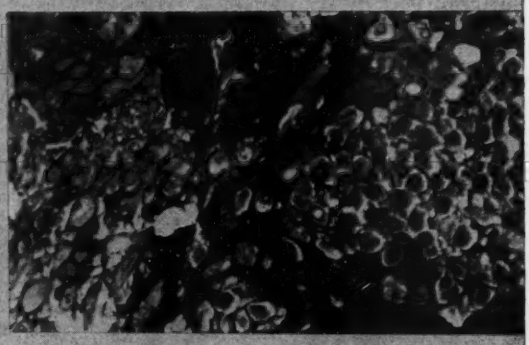

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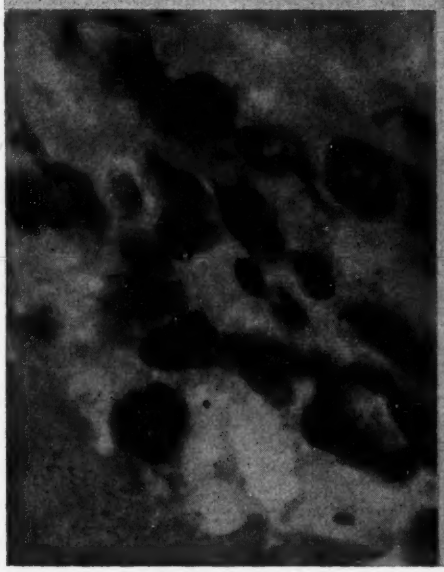

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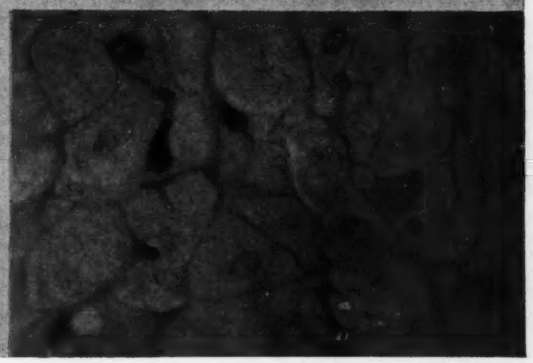

Fig. 5.

Fig. 1.—Basal plate of placenta at 6.5 weeks showing specialized trophoblastic cells with cytoplasmic metachromasia. Note the variations in size and shape of these cells. (Four per cent basic lead acetate and toluidine blue. ×610; reduced ⅕.)

Fig. 2.—Specialized trophoblast from a placenta at 6.5 months. Note the marked cellular fluidity, variations in size and shape and semisyncytial nucleated masses. Nucleoli are prominent and nuclear chromatin massed at the nuclear membranes. (Four per cent basic lead acetate and azure II-eosin. ×610; reduced ⅕.)

Fig. 3.—Specialized trophoblast from a placenta at term. Note the marked cytoplasmic basophilia, the irregularity in size and shape, and the prominent nucleoli. (Picroacetoformol and azure II-eosin. ×610; reduced ⅕.)

Fig. 4.—Basal plate of placenta at 6.5 months showing relatively chromophobic decidual cells at left and the specialized chromophilic trophoblastic cells at right. (Picroacetoformol and Masson trichrome stain. ×185; reduced ⅕.)

Fig. 5.—Decidual cells from a placenta at term showing the absence of cytoplasmic metachromasia and its presence in the matrix surrounding the cells. (Four per cent basic lead acetate and toluidine blue. ×610; reduced ⅕.)

metachromatic characteristics throughout the course of pregnancy if fixed in 5 per cent trichloracetic acid. Metachromatic granules could also be demonstrated to slight degree in the nearly chromophobic cytotrophoblast of the Langhans layer and to a greater degree in the peripheral layer of syncytial trophoblast in early stages only.

The hyaline or fibrinoid matrix in which these cells were embedded never exhibited metachromasia which is consistent with the presence of fibrin.[8] It is interesting that we found that this fibrinoid deposition began to appear in abundance at 4.5 months in regions where there were defects in the syncytial layer. It seems probable that the syncytial defects resulted from the loss of contact with material blood. Its appearance coincides with a sharp decrease in thromboplastin activity of the placenta reported by Perrini.[6] Wislocki[8] found this material to be strongly periodic acid-Schiff positive.

Comparison With the Decidual Cells

These modified trophoblastic cells are found in close relation with neighboring decidual cells of uterine mucosa and with routine methods may be easily confused with them. Some of the differential features between these two cell types have been demonstrated by Wislocki.[8] In our material the trophoblastic cells were generally smaller in size than the decidual cells, and less clearly outlined because of their delicate cell membranes. Although the nuclei of these trophoblastic cells, in the early stages, contained little DNA, chromatin increased in amount in later stages and was more closely clumped at the nuclear membranes than in nuclei of decidual cells. Nucleoli were present in both cell types but those in cells of trophoblastic origin stained more heavily with pyronin than those in decidual cells, particularly in later stages of pregnancy. Following conventional staining procedures the cytoplasm of the trophoblastic cells was more deeply basophilic than that of the corresponding decidual cells (Fig. 4). As term approached, we noted a perinuclear zone of acidophilia and peripheral zone of basophilia in the fetally derived cells which was not encountered in decidual cells. We also found the cytoplasm of trophoblast, when stained with pyronin, containing intensely pyronin-positive granules during the last trimester. Cytoplasm of decidual cells, on the other hand, in early stages showed only light stippling with pyronin or were chromophobic to pyronin. In the last trimester only the decidual cell membrane was defined by pyronin.

Cytoplasmic metachromasia as observed in the modified trophoblastic cells was not found in the neighboring decidual cells, practically no cytoplasmic staining being present in the latter (compare Figs. 1 and 5).

With the use of Bennett's sulfhydryl technique, another differential feature was the presence of highly refractile reddish granules in both nuclei and cytoplasm of the trophoblastic cells which increased with the age of the placenta. In decidual cells, such evidence of SH groups was very slight, being limited to a few cytoplasmic granules in earliest stages which were never observed after 10 weeks.

Characteristic features of the supporting matrices of these two types of cells are also different in that metachromasia is evident in the ground substance of the decidual cells and not in that of the trophoblasts. Reticular and collagenous fibers could be demonstrated only in decidual matrix. Wislocki[8] in the term placenta observed greater periodic acid-Schiff stippling (saliva insoluble) in the trophoblastic matrix as compared with that of the decidua.

Comment

The observations we have recorded lead to the conclusion that during the early stages of pregnancy groups of cells of the typical chromophobic cytotrophoblast become isolated from the cells of origin and from the maternal blood in the intervillous spaces, becoming embedded in masses of nonmetachromatic hyaline material containing fibrin. This fibrin-containing material, serving as matrix for these isolated groups of cells, was formed in all placental stages we studied and in all regions of the placenta, but was most abundant at midterm and after, in relation with frequent defects in the syncytial lining of the intervillous spaces, and when thromboplastin actually is notably decreased. Though such isolated trophoblasts are to be found throughout the placenta they are most numerous in the basal plate of the placenta and along the placental septa as Wislocki[8] has shown in the placenta at full term.

The observation of the transitional stages between typical chromophobic cytotrophoblast and chromophilic isolated groups of cells furnishes clear evidence of the origin of these latter cells. The increasing amounts of DNA and the greater prominence of nucleoli and more intense staining of cytoplasmic granules (RNA?) demonstrated by Taft's methyl green-pyronin stain surely indicate increasing metabolic activity in these special elements. With more routine stains the increasing cytoplasmic basophilia is also suggestive. Further evidence of special activity (production of chorionic gonadotropin) is to be found in the presence of metachromatic granules or fibrils in the cytoplasm of the special trophoblast cells following fixation in basic lead acetate on trichloracetic acid and staining with toluidine blue. Such metachromasia was demonstrable in the Langhans cytotrophoblast layer and in syncytial trophoblast in early stages only.

The presence of progressively increasing numbers of highly refractile reddish or orange granules in nuclei and cytoplasm of these special trophoblasts after use of Bennett's sulfhydryl reagent gives further evidence for their elaboration of some specific chemical substance. These highly refractile granules are presumptive evidence of the presence of protein-bound sulfhydryl groups probably related to the production of ACTH and chorionic gonadotropin. Although a few such thiol groups were demonstrated in the Langhans layer and in the syncytial trophoblast, it seems unlikely that these forms of trophoblast could be elaborating any significant amounts of protein hormones, such as chorionic gonadotropin.

Typical cytotrophoblast has disappeared long before secretion of gonadotropin has ceased, as this secretion continues until term.[7] The syncytial trophoblast primarily produces steroid hormones,[2, 9] which makes it difficult to conceive of it as also the producer of protein hormones.

Jones, Gey, and Gey[3] have found that chorionic gonadotropin was formed in in vitro cultures of placental cells and they thought it was produced by the Langhans layer. However, the characteristics of the cells in their cultures, such as multinuclear and semisyncytial masses, more closely resemble those of the specialized trophoblasts we have described, than do Langhans cells.

Recent investigations have shown that ACTH also is produced in large quantities by the placenta.[5] Considering the chemical nature of gonadotropin and ACTH, the specific activity of this third type indicated by the staining reactions we have observed lends additional support to the postulate that chorionic gonadotropin[8] and ACTH are secreted by these cells.

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THE PROBLEM OF SPONTANEOUS ABORTION*

IV. Further Observations on the Placental Villus

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THE histological changes found in the placental villi obtained from cases of spontaneous abortion have been described.[1] This report is an amplification and extension of the previous work.

The placentas from 114 cases of spontaneous abortion have now been examined. The controls number 55; the latter specimens were obtained from normal pregnancies terminating at various periods from the first to the ninth month. The results are shown in Table I.

Table I. Classification of Villus Lesions Found in 114 Cases of Spontaneous Abortion

	NUMBER	PERCENTAGE OF TOTAL
Lesions of abortion	81	71
Hydatidiform degeneration	3	2.7
Hydatid mole	2	1.9
Massive infarction	4	3.5
Infection	1	0.8
No lesion found	23	20.1

The problem of deciding whether the lesions of abortion precede or follow fetal death has been discussed previously, and for this reason particular effort was directed toward acquiring placentas from habitual aborters who eventually managed to have a live baby. In 4 such cases, scattered villi showed unmistakable fibrinoid lesions. As a corollary, the villi were examined from cases in which fetal death was evident, from causes other than abortion, that is, from ruptured ectopic pregnancies. The villi from 3 such cases were normal. It seems reasonable, therefore, to adduce that the lesions of spontaneous abortion do not coincide with or follow fetal death, but the proof is not yet overwhelming. The inference remains, however, that the lesions of the villi are a local expression of the aborting forces and probably play a large part in the actual termination of the pregnancy.

The staining methods used in the examination of the villi in the latter part of this investigation were hematoxylin and eosin, Masson's trichrome, toluidine blue, Mallory's phosphotungstic acid hematoxylin, Gomori's aldehyde fuchsin and Jenner-Giemsa. Material obtained from 76 abortions and 46 controls were used.

*Supported by a Federal Health Grant.

Collagen and the Placental Villus

Masson's trichrome stain renders collagen a brilliant green. In the normal placenta from a pregnancy of 3 months and under, the villus areolar network forms a delicate regular lacelike pattern as shown in Fig. 1. All the intervillus fibers including those that go to make up the blood vessel walls stain green, indicating that the entire network is composed of nothing but collagen. The blood vessel walls of the villus are formed by a thickened collagenous layer in which one to three spindle-shaped cells rest. There is no endothelial lining to be seen. Between the villus fibrils lies the ground substance.

In the placental villi from a pregnancy at term, the same collagen network is present, but the pattern is now made up almost entirely of blood vessels, with little or no ground substance. The same characteristics seen in the blood vessels in a "young" villus are present in the "old." In the latter, the vessel walls are also composed of a condensation of collagen fibrils supporting the same number of spindle-shaped cells. There is also the same lack of an endothelial lining (Fig. 2).

Fundamentally, the placental villus is composed of a collagenous scaffold around which an epithelial coat is wrapped, certainly, regarding the manifold activities of the villus, an extraordinary economy in material.

With Masson's trichrome stain the lesions of abortion vary from a proliferation of collagen causing a disruption in the regularity of the lacelike pattern to the filling of the whole intravillus space with a massive collagenous fibrillary condensation which completely ablates the normal architecture. Fig. 3 shows villi in this latter stage from a case of spontaneous abortion.

Hydatid degeneration gives an entirely different picture. The normal lacelike pattern is replaced by a breaking up of the network into diffusely spread, chaotically arranged, short strands of collagen, suggesting that some lytic agent had attacked and severed the fibrils.

Fig. 4 illustrates these changes in hydatid degeneration. In hydatid mole, the breakdown of the areolar network is complete, the intravillus space being completely filled with granular green-staining debris only.

The lesions of abortion and hydatid degeneration differ fundamentally. The first is a proliferative reaction to the stimulus which, if continued unchecked, fills the whole villus space with its exuberance; the second, a degenerative, lytic reaction, which eventually empties the space of its normal contents.

The Villus Blood Vessels

The distribution of the blood vessels within the villus has been described by Spanner[2] as a dense capillary plexus with a few short transverse connections. There are certain characteristics, however, which will bear closer examination.

Most of the vessels are subepithelial, and in many villi of moderate size the central area is entirely free of a vascular supply. This is most striking in the villi of placentas of 3 months and under, and once their basic pattern of a subepithelial vascular leash is appreciated in the "young" villus, its repetition in the "elderly" is more readily seen.

In the attempt to visualize the meaning of the changing sizes and shapes of the villus blood vessels observed in serial sections, the conception grew of an afferent vessel entering the villus base, which gave off and ended in transverse radicles at the lower levels. These transverse radicles appear to split into coiled subepithelial capillaries, in diameter slightly larger than that of a red blood cell. The subepithelial capillaries join with each other in turn to form eventually an efferent system similar to that described for the afferent.

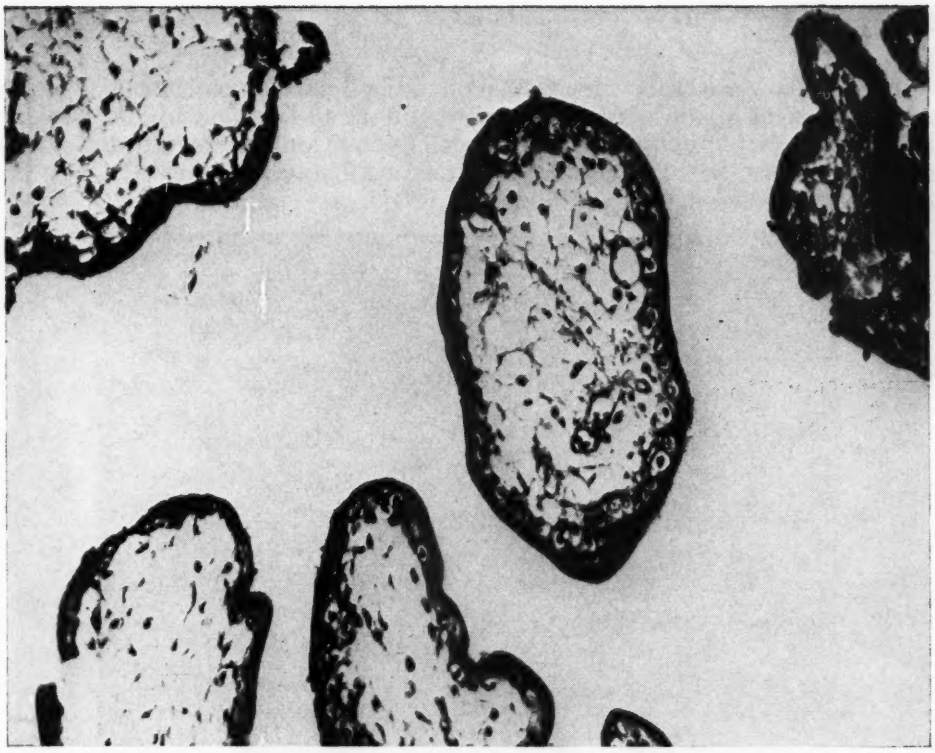

Fig. 1.—Normal villi from a 3 months' placenta showing the intravillus areolar pattern stained for collagen. (Masson's trichrome. ×170; reduced ½.)

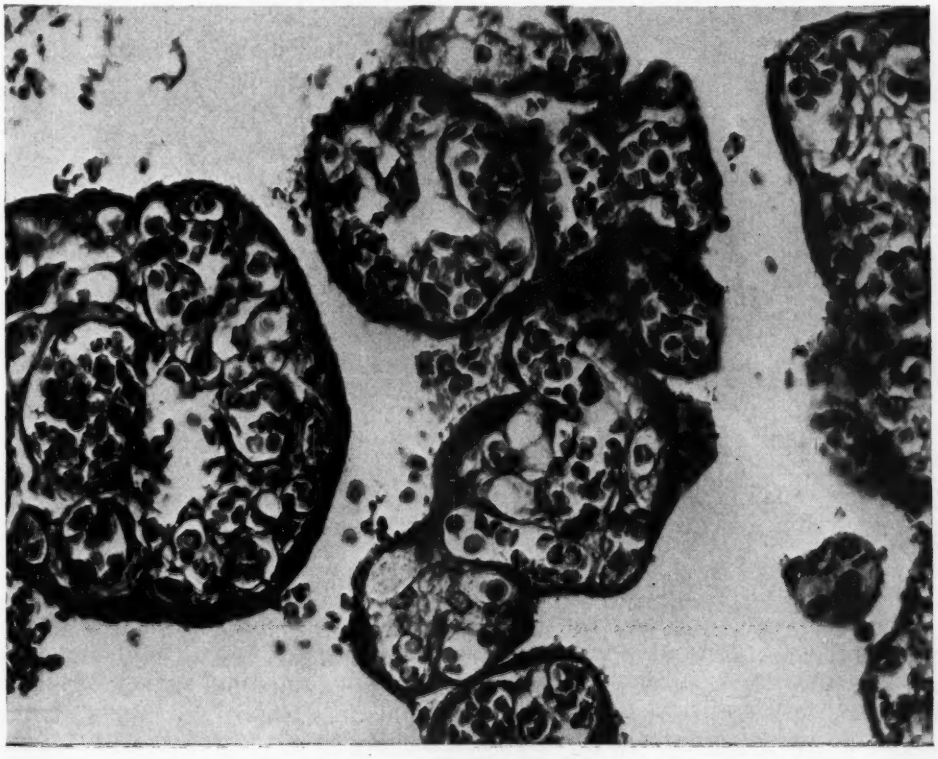

Fig. 2.—Normal villi from a placenta at term showing the intravillus pattern stained for collagen. (Masson's trichrome. ×170; reduced ½.)

Fig. 5 shows a transverse vessel in the villus of a normal 2½ months' pregnancy breaking into subepithelial capillaries. The vessels in the stalks are formed by an endothelium surrounded by a thick circular border of collagen. It appears that an endothelial layer in the vascular tree first occurs in these vessels.

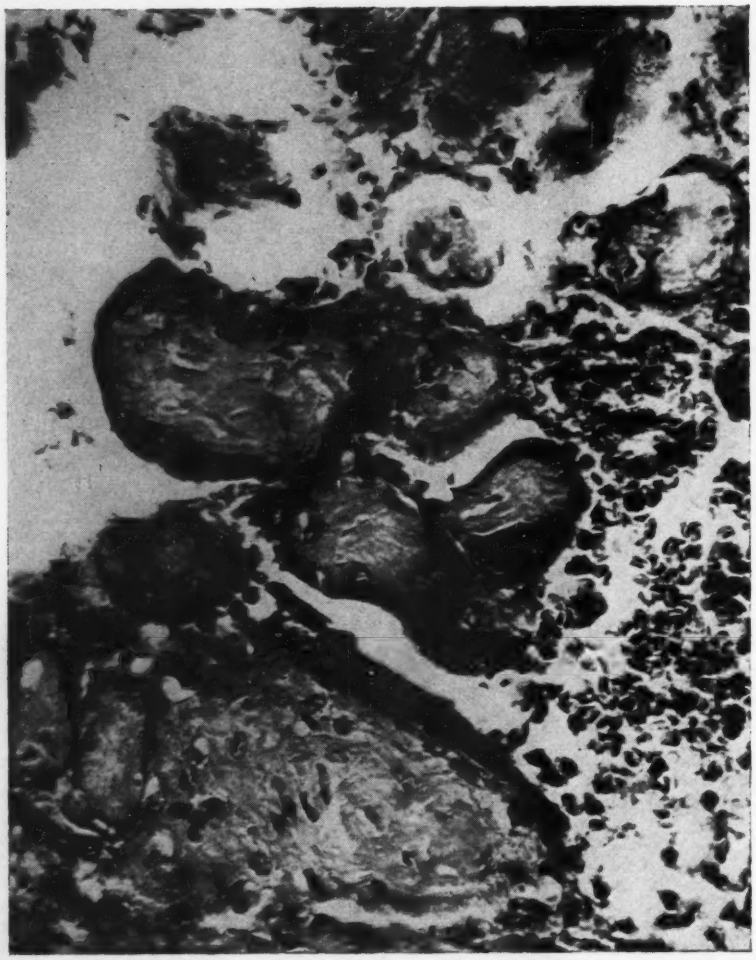

Fig. 3.—Villi from the placenta of a case of spontaneous abortion. Note the gross collagenous proliferation filling the villous space. (Masson's trichrome. ×340; reduced ½.)

It is suggested that, as the pregnancy progresses, the vessels of the villus dilate in response to an increasing blood volume with a concomitant thickening of the collagen layer of the vessel wall and an absorption of the ground substance, thus making room for the expanding vascular tree.

The Villus Stromal Cells

Javert[3] has considered the possibility that occasionally some of the aggregates of cells seen in the villus stroma may represent foci of fetal hematopoiesis. Because of this, from the material available, a critical survey of stromal cell types has been made.

In the villus of the normal placenta of 3 months and under, two types of cells can be clearly distinguished. The first and most frequent is ovoid to

spindle shaped, with a reticular nucleoplasm and scanty cytoplasm. These cells tend to lie along the axis of fibrils or group themselves about blood vessels in clusters. Stained with toluidine blue, the cytoplasm at the apex of the spindle can be seen blending into its related stromal fibril. As the pregnancy matures, the nucleus condenses and the spindle shape becomes accentuated.

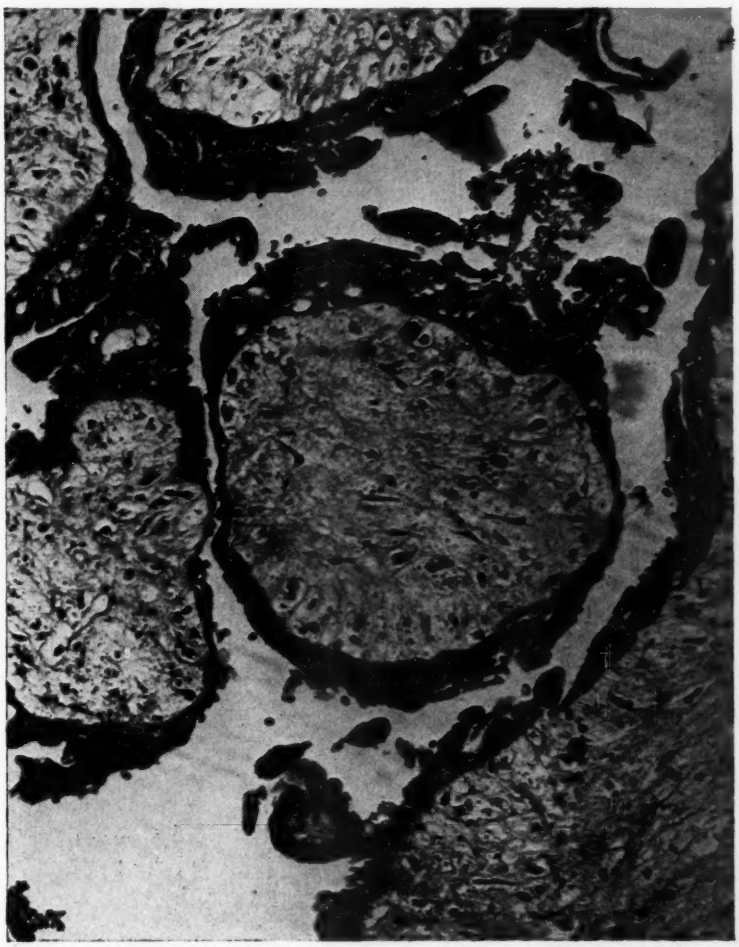

Fig. 4.—Villi from the placenta of a case of hydatid degeneration. The normal areolar network has been completely disorganized. (Masson's trichrome. ×340; reduced ½.)

The intimate relationship between these cells and the collagen fibrils of the villus areolar network suggests that they are primarily responsible for its development and increase.

In spontaneous abortion there is a marked proliferation of the spindle cells in the early phases of collagen response to this disease, and in the final stages of complete collagenization and hyalinization, the spindle cells die.

The second type seen in the villus network of a placenta of 3 months and under is the so-called Hofbauer cell. Once past the first trimester, this cell vanishes, leaving the spindle cell dominant. The Hofbauer cell has a round, homogeneous, dark-staining nucleus, lying eccentrically in an abundant cytoplasm. The cytoplasm is finely granular, red with periodic-acid-Schiff reagent, acidophilic with the Romanovski stains, orthochromatic to toluidine blue, and

agranular with Gomori's aldehyde fuchsin stain. When observed within the villus, it most often appears to have attached itself to a fibril by its cytoplasmic border with the remainder of the cell lying in the adjacent ground substance. The villus shown at the upper left-hand border of Fig. 1 exhibits several Hofbauer cells clearly. What their function may be is not clear, but it is generally held that they are tissue phagocytes. It may well be that they have phagocytic properties; if so, it must be a very minor function, for in all the specimens examined, I have not seen one in which the cytoplasm contained ingested material. They are not mast cells, for the cytoplasm is orthochromatic

Fig. 5.—Villus from a normal placenta of 2½ months' pregnancy showing an intravillous blood vessel in the form of a transverse radicle breaking into subepithelial capillaries. (Masson's trichrome. ×340; reduced ½.)

with toluidine blue, and dark granules do not appear after staining with Gomori's aldehyde fuchsin. Morphologically, these cells resemble histiocytes, a term which is more acceptable than tissue phagocytes for it broadens functional conception. The histiocytic cell can react to local tissue trauma or it can differentiate into a fibroblast, if so required. Such a transformation into a fibril-producing cell may be seen in the villi from some cases of spontaneous abortion. Between the earliest change so far noted—that is, ground substance

metachromasia and the frank collagenous proliferative phase—there is an intermediate state in which histiocytes show a marked increase in cytoplasm from which stream long erratic filaments into the ground substance. Both the cytoplasm and the cytoplasmic filaments stain a deep pink with the periodic-acid-Schiff reagent, with which the histiocytic activity is best seen. The picture presented suggests that this fine erratic reticulation is a precursor of the formation of the thicker collagen fibers whose coalescence makes the collagenous plaques. With the formation of the collagen masses the histiocytes disappear.

An extensive search of many villi stained with Jenner-Giemsa from both normal and abnormal placentas of all ages has so far failed to reveal any areas of hematopoiesis.

Fibrin and Fibrinoid

Fibrin is derived from the precipitation of converted plasma fibrinogen; fibrinoid, on the other hand, occurs in areas of collagen necrosis and its nature differs fundamentally from that of fibrin. The difficulty of separating them by tissue stains is somewhat laborious, but essential. By the use of toluidine blue, Mallory's phosphotungstic acid hematoxylin, and Weigert-Gram iodine, a reasonable decision can usually be made into which category a deposit under examination falls.

In the placenta the term fibrinoid has been used to designate that substance found surrounding an occasional villus, often accompanied by hyalinization of the particular villus attacked. This term appears to be a misnomer, for Singer and Wislocki[4] have shown that the material in question is true fibrin. Similarly, the massive intervillus deposit that accompanies white infarction is also fibrin. On the other hand, the necrosis that follows upon the later stages of villus collagenosis in the lesions of abortion shows metachromasia, a golden brown color to Mallory's stain and blue to Weigert-Gram iodine. Fibrin with these stains in the same order is orthochromatic, deep blue, and purple. There seems to be little doubt, therefore, that true fibrinoid necrosis occurs in these lesions.

Comment

The fundamental part played by collagen in the villus architecture was not properly appreciated until Masson's trichrome stain was incorporated among the routine procedures used in this study. It is not surprising, therefore, that lesions of this functional unit are so often reflected by a derangement in its collagen structure. In syphilis, spontaneous abortion, and perivillus fibrin deposit, the primary irritant brings about a proliferation of the collagen network. In hydatid degeneration, hydatid mole, and to some extent eclampsia, the stimulus results in disintegration of the areolar network. It appears that, tumors aside, this short-lived organ, composed of simple and economical tissue and achieving complex functions in spite of simplicity, reacts to noxious irritants in two ways only—a reflection of its unique histological composition.

It is generally agreed among obstetricians that the incidence of congenital anomalies is much higher in the fetuses of abortion than in the infants born of normal pregnancies. It has been argued that the congenital defects may be the causal factor in abortion. The conviction has grown, however, as an outcome of this work, that pathological alteration in villus ground substance or stromal network is a basic factor in the pathogenesis of the vast majority of

the cases of abortion. Where or what its predecessor is at present must be entirely speculative. An argument in favor of the view that congenital abnormalities are secondary to pathological changes in the villi follows upon the work of Schreier.[5] He has shown that the growing fetus is avid for amino acids, the demand being greatest in the youngest and smallest fetus, tapering away as maturity is reached. Furthermore, the placenta has the capacity of concentrating amino acids in the direction of the fetal circulation. It follows, then, that if there is a decrease or failure in both quantity and quality in the transmission of amino acids, protein synthesis must be slowed to the level of what is available. In its simplest terms, gross variation in the amino acid pattern should be followed by gross alteration in the protein cellular pattern—hence, "congenital abnormalities."

Summary

1. Metachromasia in the villus ground substance and/or proliferation of the villus collagen network has been found in 71 per cent of the placentas from cases of abortion.

2. The role of collagen in the villus areolar network has been stressed.

3. The histology of the villus has been reviewed.

4. The relationship between villus pathological changes and fetal congenital abnormalities has been discussed.

I am indebted to Dr. Carl Tupper for the material provided, to Mr. J. A. Rowse for much technical assistance, and to Mr. J. Merriman for the photographs.

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THE ABNORMAL VAGINAL SMEAR IN ABORTION*

A Controlled Study of Progesterone Therapy

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IN 1954 the author[11] published a statistical study suggesting that many abortions could be predicted in early pregnancy by noting certain changes in the vaginal cytology. These changes are an increase in the acidophilic, mature, estrogenic, or superficial type of cells, and a decrease in the basophilic, premenstrual, or intermediate type of cells usually in preponderance in early pregnancy. We were not original in this thought. Schuman,[21] in 1944, called attention to a change in vaginal cytology in threatened abortion. His conclusions have not been verified by later investigators. Hall,[5] in 1945, noted the vaginal cytological changes typical of threatened abortion. Several others since have verified and amplified his findings.[2, 4, 7, 9, 12, 16, 18] I would suggest that persons interested in this subject read the European and Latin-American literature, particularly the works of Pundel and van Meensel,[13] Kamnitzer,[7] and Rodrigues Lima.[18] These contain much fundamental information which has been missed by American writers.

Papanicolaou and Shorr,[10] in 1936, showed the effect of estrogen on the vaginal cytology. Shorr,[22] in 1940, showed that the cytology of pregnancy was due to estrogen plus progesterone. Since then it has been generally accepted that a preponderance of superficial cells in a smear means a deficiency of progesterone in relation to estrogen. We have assumed then that these abortion-prone women with a mature type of smear had a deficiency of progesterone. We do not know whether this deficiency is primary (defective corpus luteum or poor uterine environment) or secondary (defective ovum). When the progesterone deficiency or the changes due to it are reversible, a significant increase in fetal salvage should be noted if these women are treated with progesterone.

To test this hypothesis the author conducted the following study. Vaginal smears were obtained from 600 women during the first four months of pregnancy. These were interpreted and women with more than 30 per cent mature cells were given either progesterone Lingusorbs,† 25 mg., or identical placebos, taken by buccal absorption, one daily, until four and one-half months of pregnancy. This was a blind study. The office nurse distributed the bottles which

*Presented at a meeting of the Minnesota Obstetrical and Gynecological Society, St. Paul, Minn., Dec. 3, 1955.

**Present address, Pikeville Memorial Hospital, Pikeville, Ky.

†Progesterone Lingusorbs and placebos for this study were supplied by Ayerst Laboratories.

were identified by number only. The key to the numbers was available to no one until after the study was completed. Smears were repeated at intervals of one month or more in 21 cases selected at random which had increased mature cells on the first smear. Specimens for pathological examination were obtained from 14 patients who aborted.

The smears were obtained by gently wiping a tongue blade along the anterior cervix from the anterior fornix downward, with care to avoid any areas of erosion. This was spread on a perfectly clean glass slide and immediately immersed in 95 per cent ethyl alcohol for 90 minutes. Care must be taken not to leave the slide in alcohol too long as this causes too much desiccation and false eosinophilia. The staining technique* was a modified Papanicolaou cytological stain. Our interpretation of the smear is based more on qualitative than on quantitative factors. Our European and Latin-American colleagues employ definite indices of eosinophilia and pyknosis. In our interpretation, morphological characteristics are more important than color reaction. The large, flat cell with a dark, small nucleus is classed as more mature than normal, regardless of color. Figs. 1 and 2 are examples of the normal and abnormal cells, respectively.

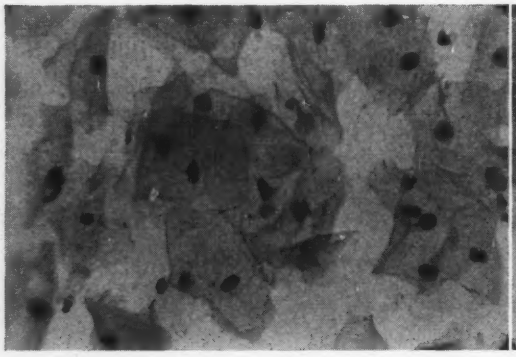

Fig. 1.

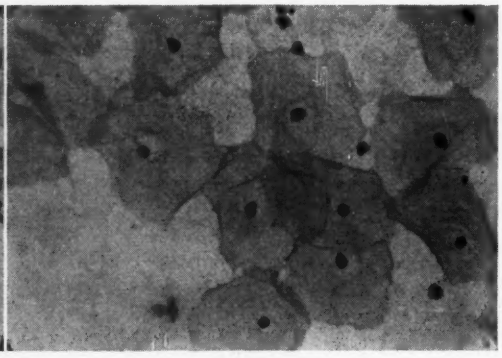

Fig. 2.

Fig. 1.—The type of epithelial cells normally seen in early pregnancy. Most of these cells are basophilic.

Fig. 2.—The abnormal or more mature type cells seen early in some pregnancies likely to be aborted. These cells are mostly acidophilic.

Results

Refer to Table I for the tabulated results of this study. Seventeen cases were deleted for the following reasons: records were lost; the patient moved away; the number of the bottle was not recorded.

TABLE I. PREGNANCY OUTCOME RELATED TO TYPE OF SMEAR AND TYPE OF TREATMENT

	TOTAL CASES	ABORTIONS	BLEEDING (UP TO 7 MONTHS)	ABNORMALITIES ATTRIBUTED TO PLACENTA (AFTER 7 MONTHS)
Normal smears (30% or less superficial type cells)	424	15 (3.5%)	35 (8.2%)	19 (4.7%)
Abnormal smears (30% or more superficial type cells)	159	11 (6.6%)	39 (24.5%)	17 (12.4%)
Abnormal, treated	76	5 (6.5%)		7 (10.1%)
Abnormal, not treated	83	6 (7.2%)		10 (14.5%)

*Credit is due to Marian M. Ambrose, B.A., M.S., of the clinical laboratories of the Lenont-Peterson clinic, who gave much valuable help in the staining and screening of these slides.

The abortion rate was very low. I do not know the reason for this. Our previous work and that of others was confirmed by the fact that the abortion rate in those with abnormal smears was double that of the normal group (7.2 per cent versus 3.5 per cent). Progesterone in the dosage and form used was not significantly effective in increasing fetal salvage in the group with progesterone-deficient smears (6.5 per cent versus 7.2 per cent abortion). Those with abnormal smears had a greater tendency to bleed up to 7 months (24.5 per cent versus 8.2 per cent). Pregnancy difficulties after 7 months attributable to placental abnormalities (premature separation, placenta previa, circumvallata, premature aging) were significantly more common in the group with abnormal smears. Progesterone therapy during the first four and one-half months did not significantly reduce the incidence of the late placental difficulties.

Smears were repeated in 21 cases which originally showed over 30 per cent mature cells. These were taken from 1 to 3 months after the initial smear. Of the 12 receiving progesterone all showed improvement, that is, a decrease in the number of superficial cells and a corresponding increase in the intermediate or normal cells. Of those taking placebos (9), all but one showed definite improvement in the smear. This is not necessarily significant since the really irreversible smears were probably missed by waiting at least one month for a repeat. The patients had already aborted. This, however, emphasizes Pundel's[14] observation that a large number with abnormal cells will revert to normal without any treatment. He attributed this to a persistence of the normal hormone rhythm in early pregnancy. There is an increase in the mature cells at the time which would correspond to ovulation if pregnancy had not intervened. There is also apt to be an increase in mature cells at about 3 months of pregnancy. This corresponds to the time of transfer of hormone production from ovary to placenta. These changes are quickly reversed in a normal pregnancy. It, therefore, becomes evident that, to get definite evidence of progesterone deficiency, one must follow the patient with serial slides at close intervals and correlate the smears with the duration of pregnancy. This was not done in this study and may have influenced our results. A smear which returns to normal following progesterone therapy does not necessarily mean a reversal of the pathological condition. The normal smear may be due only to the local effect of progesterone on the vaginal mucosa.

Specimens for examination were obtained in 14 of the 26 abortions. These were examined for signs of degeneration, indicating poor placental hormone function for a period of several weeks before abortion.[3, 20] Of the abnormal smears treated with progesterone, only one specimen was available. This showed poor placental function, a degenerated fetus, hydropic degeneration of villi, and only scattered areas of placenta about the sac. Of the abnormal smears not treated (placebos), 3 valid specimens were obtained. They showed long-standing necrosis and degeneration. From the patients who had normal smears and aborted, 6 specimens suitable for examination were obtained. These showed slight edema, a few scattered areas of degeneration, and 1 case with only one layer of trophoblast. Abnormal smears were associated with markedly degenerated placentas while normal smears were associated with much less placental degeneration.

Comment

Progesterone deficiency as shown by the vaginal smear seems to be a factor, either cause or effect, in many abortions. Progesterone is produced by the corpus luteum and later by the trophoblast. The progesterone from the

corpus luteum supports a good environment (endometrium) for implantation and early growth of the trophoblast. A healthy trophoblast in turn produces chorionic gondotrophin which prolongs the function of the corpus luteum and hence its production of progesterone. Later a good trophoblast itself produces progesterone. This is environmental influence. Another form of progesterone deficiency may occur because of an abnormal ovum which is unable to form a normal trophoblast in spite of good early environment. This results in a deficiency of gonadotrophin early, and of progesterone later. This study was undertaken with the idea that some of these progesterone deficiency states might be reversible if treated with progesterone early in pregnancy. In the form and dosage used, progesterone was of no value. Randall and co-workers[17] have reported, in an uncontrolled study, that stilbestrol given in early pregnancies with abnormal smears did not significantly increase the fetal salvage. It still seems logical to assume that there must be some of these cases in which the changes are early and minimal. Progesterone might produce a desirable environment and salvage the pregnancy. Pundel[15] suggested a method for separating those with abnormal smears into two groups: those with a living trophoblast capable of responding to therapy, and those with a degenerated trophoblast incapable of responding. His method of separating these is as follows: Stilbestrol is given to all those with abnormal smears. He has found that those who are apt to recover will show a reversion of the smear to normal in a short time. Those who are not apt to recover will show an increase in the abnormality (increased maturity).

Some increase in salvage might be obtained in the group of pregnant women with abnormal smears by using Pundel's test of viability and then by giving progesterone in larger doses, perhaps intravenously as suggested by Karim and Wahba.[8] Whether this is practical or not is another question to consider. It appears that more and more support is building up for the contention that environmental factors are important in abortion. The suggestion of Rutherford,[19] and later Hughes,[6] for preconceptional correction of these environmental factors is assuming added importance. Preconceptional therapy is practical only in cases of habitual aborters. Colvin[1] has reported that bed rest alone is as effective as any other treatment in threatened abortion. It seems that the day of the indiscriminate dosing of patients with threatened abortions with hormones is closing.

Conclusions

1. A study of the vaginal cytology in 583 women in early pregnancy is presented.

2. Previous reports that those with abnormal smears are more apt to abort were confirmed.

3. Those with abnormal smears were treated with progesterone or placebos (blind control). Progesterone, 25 mg. daily by the buccal route, is not effective in salvaging pregnancies in this abnormal group.

4. Those with abnormal smears in early pregnancy are more apt to have late pregnancy difficulties due to placental abnormality. Progesterone in early pregnancy did not significantly decrease the incidence of these difficulties.

5. The unsuccessful attempts of others to salvage pregnancies in this abnormal group by treating with stilbestrol is cited.

6. It is suggested that only by providing a good preconceptional environment can we improve the salvage rate in threatened abortion. For obvious reasons this is not practical except in those who present themselves for preconceptional study.

7. The stilbestrol test of Pundel and van Meensel is suggested as a good prognostic test in cases of threatened abortion.

8. The indiscriminate treatment of threatened abortion with hormones is condemned.

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UTERINE MOTILITY IN THE SECOND TRIMESTER

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(From the Allmanna Barnbordshuset)

DURING the nearly one hundred years since study of uterine motility was initiated, a number of methods for measuring and recording it have been devised. They are divided into two groups, the external and internal methods.

The external hysterographic techniques have included the Crodel[1] tokometer, Dodek's[2] pneumatic hysterograph, Frey's[3] hysterotonograph, the Lorand[4] and Reynolds[5] tokodynamometers, and various electrohysterographic methods.[6-11] More investigators in this sphere include Schaeffer,[12] Bukoemsky,[13] Rübsamen,[14] Fabre,[15] Embrey,[16-17] Murphy,[18] and others.

The internal recording methods have consisted of various intrauterine balloons, bags, and catheters, uterine cavity and uterine muscle electrodes to record activity potentials, hysterosalpingography with various contrast media, microcarbon pressure receptors, transabdominal and transvaginal intra-amniotic pressure manometers, uterine intramuscular microballoons, and different types of intrauterine electrical strain gauges. Many prominent names are included in this field.[19-39]

Of all these methods, one of the most accurate and efficient, and judged by Jeffcoate[40] to be one of the very best, is that of Karlson.[35] This is an internal technique and the apparatus consists of a receptor probe, the recording instruments, and electrical batteries. The receptor probe (Fig. 1) is constructed of soft steel wire 30 cm. in length and 1 mm. in diameter, to which are soldered three receptor chambers, positioned on the wire so that one each will be located in the fundus, isthmus, and cervix. These chambers are composed of two copper caps on either end of a short rubber tube which contains packed carbon powder; the chambers are cylindrical and measure 12 mm. in length and 4.5 mm. in diameter. From each chamber two conducting wires pass along the receptor probe to their respective terminals.

The three small carbon chambers via their direct contact with the uterine walls give a recording of the extent and progress of motility in various parts of the uterus. Every increase in intrauterine pressure causes a decrease in the electrical resistance of the carbon which produces an increase in the current which is passing from batteries to three self-registering milliammeters, each one electrically connected to its respective carbon chamber in either the fundus, isthmus, or cervix. Each milliammeter is equipped with an ink recording system and registers on a graph which rotates at a speed of 6 cm. per

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minute. The sensitivity of the receptor chambers and the recording apparatus is such that distinct deflections are obtained for variations in pressure of approximately 1 mm. of mercury.

Purpose of Study

Knowledge of the physiology of the pregnant uterus in the first six months is scanty, primarily because research has been nearly completely curtailed by the possibilities of jeopardizing the fetus by the methods of internal hysterography. External tokometry is not feasible in the first two trimesters because of the smaller size of the uterus. In Sweden, however, opportunities are available to study uterine physiology during pregnancy by utilizing for clinical research those patients admitted to the hospital for legal abortions; legal abortions here are relatively frequent and are usually performed between the tenth and twenty-fourth weeks of pregnancy. When a patient is studied in the hospital just a few hours prior to surgical interruption, no significance is attached to inadvertent rupture of membranes, initiation of fetal distress, or induction of labor, if such does occur as a result of the investigative technique.

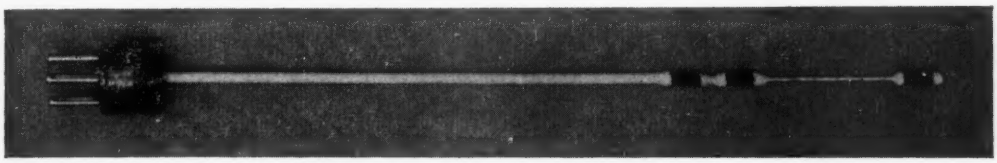

Fig. 1.—Receptor probe.

We considered that a study such as this could be valuable in contributing hitherto unavailable information and data to the realm of physiology of the pregnant uterus. Evidence concerning myometrial activity in pregnancy is of basic importance in solving clinical problems such as spontaneous abortion, habitual abortion, missed abortion, premature labor, and the eventual full understanding of normal and abnormal labor.

Material

From a total of over 100 pregnant women admitted to the Allmänna Barnbördshuset (The General Maternity Hospital of Stockholm) during 1955-1956 for legal abortion, 55 whose gestations seemed normal in all respects and who wished to cooperate in this study were selected for recording.

The patients' ages ranged from 15 to 43. The series included 10 women pregnant for the first time and 45 women who had at least one child.

The patients' pregnancies varied in time of gestation from 10 to 24 weeks; the length of each gestation was measured in weeks from the first day of the last menstrual period. Table I shows the distribution of primigravidas and multiparas and also the distribution of cases per number of weeks of pregnancy. The heavy concentration of patients between the seventeenth and twentieth weeks is due to the average 6 week delay from the time of request for interruption by the patient (usually after the second missed period) to final governmental approval after clearance of the request by the various social, medical, and psychiatric bureaus.

Technique

The patient was usually studied on the second hospital day, a few hours before surgical interruption of the pregnancy was contemplated. After catheterization, a careful abdominal and pelvic examination was done and if no abnormalities were detected, the procedure was begun. A speculum was inserted in the vagina, the cervix grasped with a tenaculum, and a sterilized, calibrated receptor probe passed gently upward between the membranes and the uterine wall until the graduated scale on the receptor probe indicated that the carbon chambers were located at the fundus, isthmus, and cervix, respectively. Dilatation of the cervix was never required and no premedication, analgesia, or anesthesia was ever necessary for this procedure. Before insertion of the receptor probe, each carbon chamber was calibrated for sensitivity in the apparatus described by Karlson[35] in his original paper.

The patient lay quietly and comfortably in the supine position during the study period (at least two hours). One of us was in constant attendance on the patient to note motility patterns and any artifacts produced by her movements. There were no complications in any of the 55 cases. In no patient were the membranes ruptured, bleeding induced, or fetal distress encountered; no uteri were perforated, labor was not initiated, and no infections developed as a result of these intrauterine investigations.

TABLE I. DISTRIBUTION OF GRAVIDITY AND MOTILITY PATTERNS PER WEEK OF GESTATION

	WEEKS PREGNANT													
	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Motility Pattern No. 1.— 26 patients														
Primigravidas								3	1	2				
Multiparas				1	1	1		6	2	3	2	2	1	
Motility Pattern No. 2.— 15 patients														
Primigravidas								1		1				
Multiparas		1	1	1	1	2	2	1	2	1	1			1
No Motility Observed.— 14 patients														
Primigravidas					1				1					
Multiparas	1				1	1	1	1	4	2	1			
Total 55 patients	1	1	1	2	4	4	3	12	10	9	4	2	1	1

Findings

The findings in these recordings are artificial to a certain degree since the receptor probe is inside the uterine cavity throughout the 2 hour study period, but are as nearly physiologic as can be attained with the methods of investigation available today. All artifacts (from the patient's movements, palpation of the abdomen, auscultation of the fetal heart, etc.) were excluded in the interpretation of the registrations. The motility recorded during the first 15 minutes was disregarded, for in all cases it required approximately 5 to 10 minutes for the "irritation motility" initiated by insertion of the receptor probe to subside.

No myometrial activity was evident in 25 per cent of the patients investigated (14 of 55 women). In these cases the quiescence was practically complete except for an occasional small contraction in one of the three regions of the uterus. During the 2 hour study periods of these inactive uteri, no abnormalities were detected in the recording apparatus; the possibility of insensitive or malpositioned receptor chambers was excluded in each case by

giving a minute dose of an oxytocic drug just prior to termination of each study, to stimulate uterine activity and, by recording this drug-induced motility, to demonstrate that the receptor chambers could function adequately (Fig. 2).

A majority of the patients studied (41 of 55 women) showed definite uterine motility. Nevertheless, in these cases it was not uncommon for periods of activity to be interspersed by intervals of very little motility or actual quiescence. Two different types of myometrial contraction patterns were observed.

One motility pattern was observed in 15 patients and is demonstrated in Fig. 3. These patterns consisted of high tonus with superimposed contractions of small amplitude and short duration (2 to 4 seconds) and a frequency of one every 3 to 6 seconds; they were very similar in both fundus and isthmus. Cervical activity was negligible in these women.

The more frequent of these patterns was noted in 26 women and is demonstrated in Fig. 4. These recordings exhibited synchronous fundal and isthmic contractions of approximately 30 to 60 seconds, occurring every 2 to 3 minutes, and possessing an average amplitude in the fundus of 12 Ma. of current which is comparable to approximately 100 mm. of mercury.* Tonus was usually absent, and if present was usually slight in both the fundus and isthmus. Little cervical activity was ever noted.

In both the active and inactive groups there was very rarely noted an isolated, spontaneous contraction, synchronous in fundus and isthmus and lasting 40 to 60 seconds. These were identified as Braxton Hicks contractions which Kaiser[41] reported were present in 75 per cent of patients who were at least 27 weeks pregnant.

Fetal movements were frequently recorded and appeared as typical short (one second) deflections of large amplitude; they were corroborated by the patient at the times of their appearance.

In both patterns cervical activity was usually slight if present, and was comprised of small deflections with no pattern and no relationship to fundal or isthmal motility.

Analysis of the cases in the active and inactive groups discloses no relationship of motility to parity, age, or number of weeks of pregnancy (Table I).

Comment and Conclusions

The comparison of uterine activity in animals and that in humans is interesting. Recording of myometrial motility during early phases of pregnancy has been done in rabbits. The uterus duplex of a rabbit shows irregular contractions, segmental in various parts of the uterus, during the first week.[42] Thirty-two days is the normal length of gestation. From the tenth to the twenty-third day there is practically no uterine motility in the rabbit.[43] This corresponds to the second trimester in women, in whom we have found no uterine motility in only 25 per cent. From the twenty-fourth day on, the uterus of the pregnant rabbit shows increasingly vigorous contractions, eventually merging into coordinated labor[44] similar to the process in women as reported by Delson and associates.[45]

The few reports in the literature on human uterine motility in the second trimester contribute only scanty information. In 1944 Malpas,[46] during laparotomies for therapeutic abortions, visualized and described uterine motility

*The calibration of each of the receptor chambers both prior to and after the recording in a patient gives a quantitative determination of the intrauterine pressure as expressed in milliamperes per millimeter of mercury. With carbon, however, the curve of pressure rise with time and the curve of electrical conductance increase are not superimposed on one another, so that only an approximate relationship can be drawn between the amplitude of the contractions as measured in milliamperes of current and the millimeters of mercury pressure correspondent to that current as determined in the calibration apparatus.

Furthermore, exact quantitative recordings are precluded because the area of contact of the receptor chambers with the uterine walls in the fundus, isthmus, and cervix is not known.

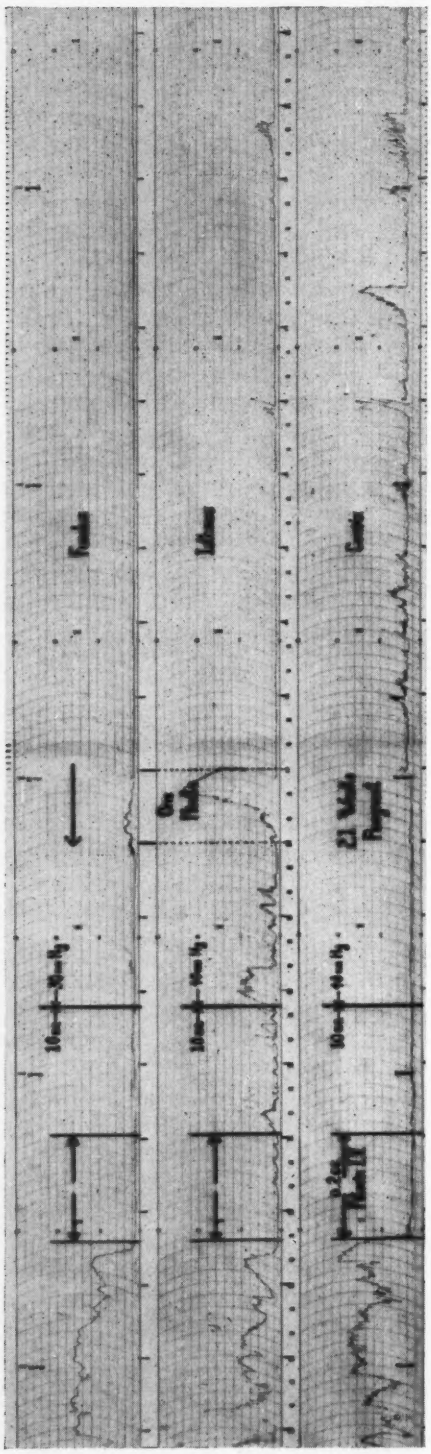

Fig. 2.—Pregnant uterus at 21 weeks, inactive. Stimulation by Pitocin.

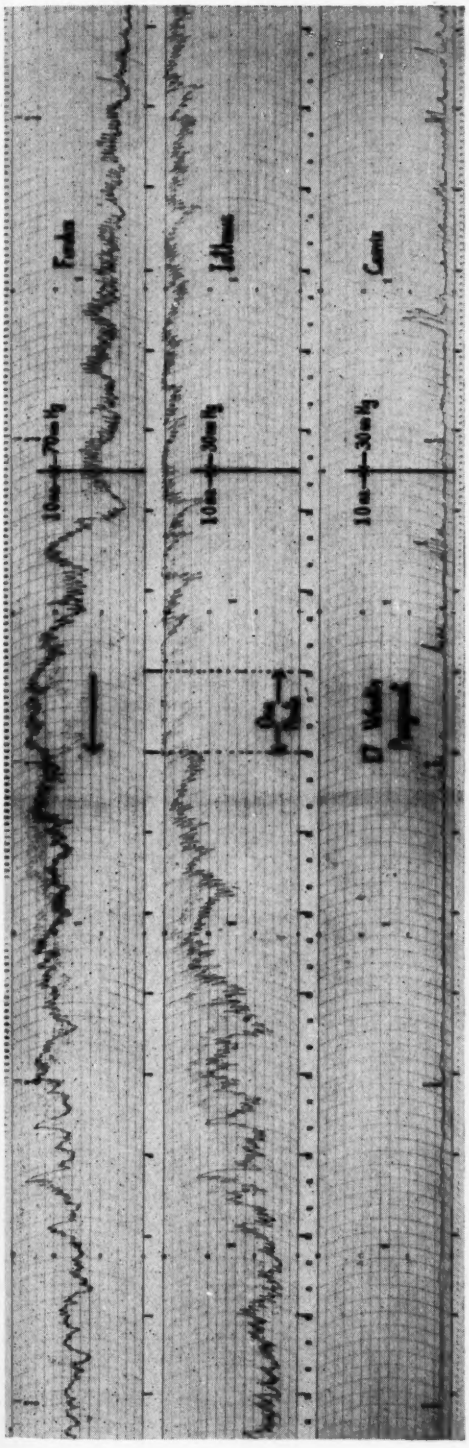

Fig. 3.—Pregnant uterus at 17 weeks, active. Pattern No. 2.

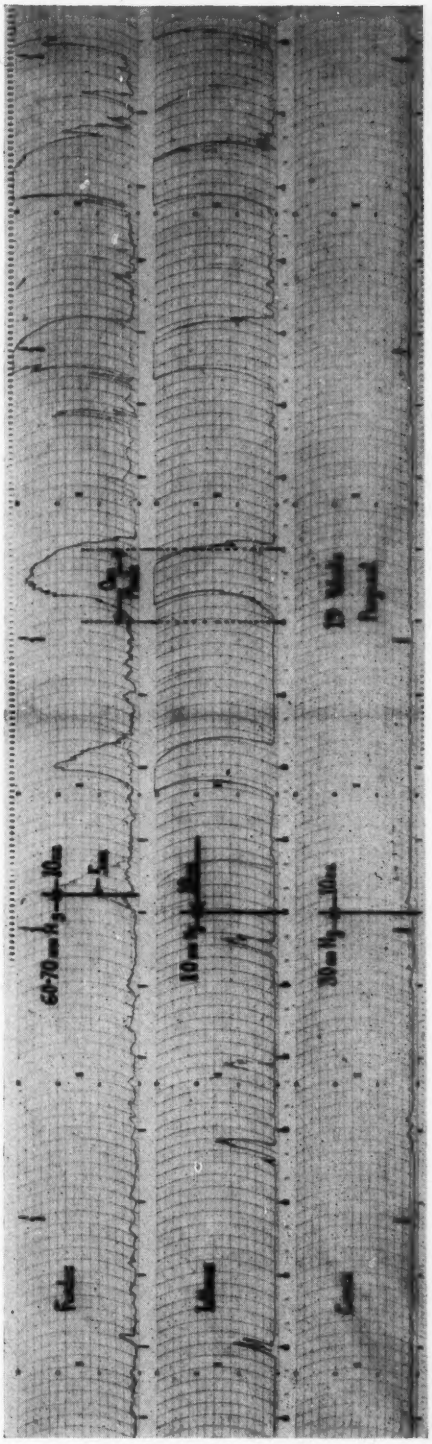

Fig. 4.—Pregnant uterus at 19 weeks, active. Pattern No. 1.

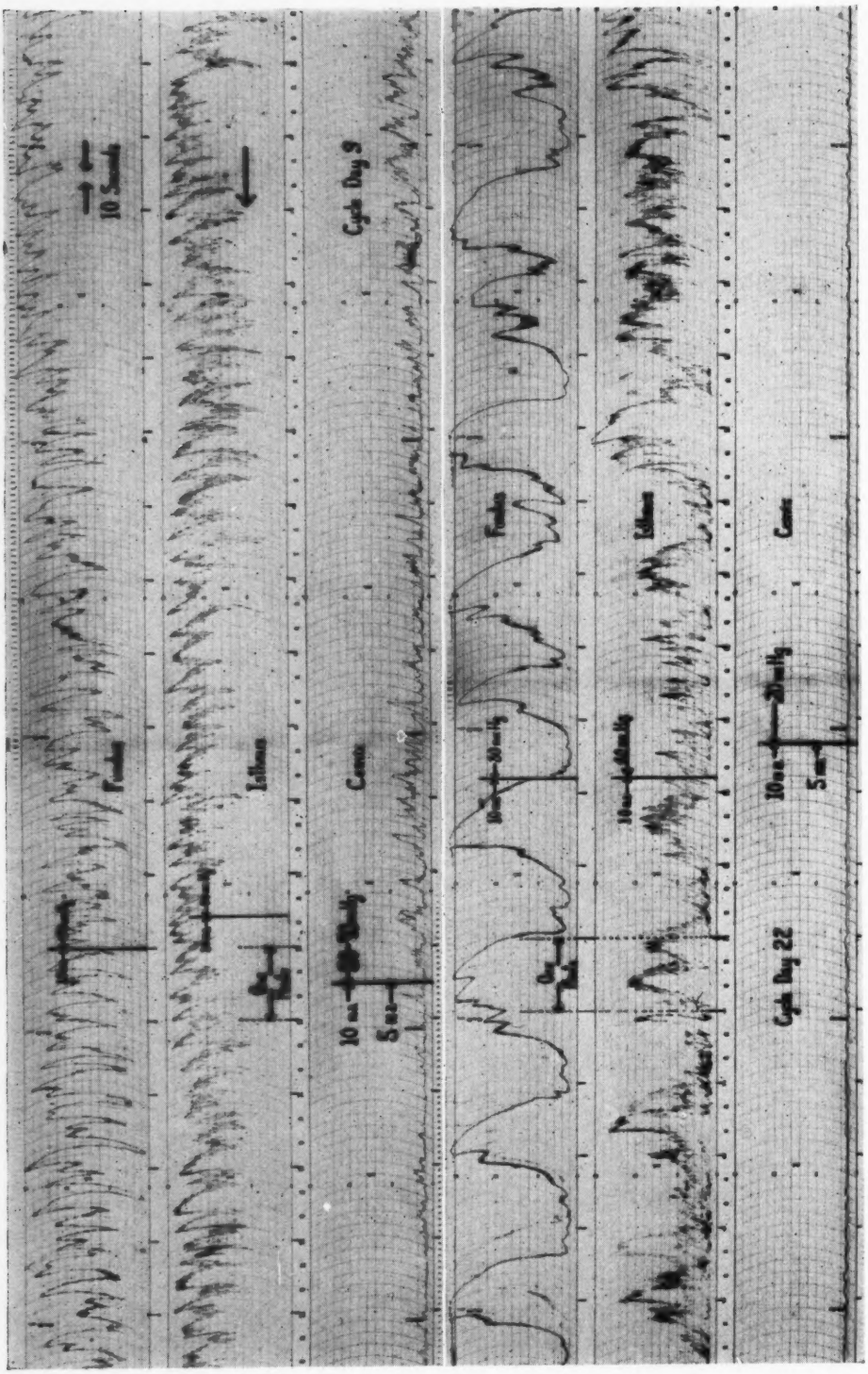

Fig. 5.

Fig. 6.

Fig. 5.—Cycle day 9. Proliferative phase pattern.
Fig. 6.—Cycle day 22. Secretory phase pattern.

patterns in 18 patients; he attributed this contractility to the spinal anesthesia which these patients had received. The same year Moir[32] inserted an intrauterine condom in 6 patients who had had premedication for therapeutic abortion via hysterotomy and noted feeble contractions which disappeared when the cyclopropane anesthesia was initiated.

In 1947 Murphy[18] from studies with the Lorand tokograph reported that, in 19 women investigated between the sixteenth and twenty-fifth weeks of pregnancy, he found only one case which exhibited uterine contractility. The high degree of insensitivity of external tokography before the twenty-fourth week of pregnancy casts doubt upon this report.

Alvarez and Caldeyro-Barcia[47] in 1950 inserted transabdominal catheters into the amniotic fluid and recorded uterine motility in a few cases in the second trimester. They reported that these cases showed the same findings as their cases studied in the last trimester (up to the thirty-eighth week), namely, continuous rhythmical contractions appearing without any intervals of rest, a frequency of one to three per minute, and an intensity of only 5 to 40 mm. of water plus moderate tonus of from 40 to 100 mm. of water (13 mm. H_2O = 1 mm. Hg). Their findings are subject to question because of their slow recording speed (0.5 cm. per minute), the errors always associated with very sensitive methods (contractions of 5 mm. of water), the inability to record rapid contractions due to the inertia associated with fluid manometers, and the inability to record activity in different parts of the same uterus. Furthermore, we doubt that any physiologic activity such as uterine motility will show no degree of variation throughout a 30 week period as is asserted by these authors.[47]

Schild and associates[38] in 1951 studied 24 patients (with premedication for abortion by hysterotomy) with triple intrauterine balloons and noted occasional spontaneous contractions in both the fundus and cervix which were out of phase with one another; no additional information on the contractility was reported.

The results of our studies show that the majority of uteri in the second trimester exhibit definitive patterns of motility. It is unlikely that the contractility patterns are a manifestation of "foreign-body reaction" for the irritability deflections were typical in appearance with very high tonus, and disappeared in all cases within 10 minutes from the beginning of the registration. The motility patterns were not persistent in each patient as there were frequent intervals of inactivity and quiescence. As far as could be ascertained, when the contractions occurred they were not related to or associated with fetal movements, changes in patient or receptor probe position, abdominal pain, urge to void or defecate, hunger, weariness, or other symptoms.

Interpretation of the two motility patterns is difficult and one can only conjecture as to what may be the significance of an active uterus during the second trimester; furthermore, the fact that one of every 4 patients exhibited absolutely no evidence of myometrial activity during the study period is unexplained. Caution is necessary in drawing conclusions from observations of a pregnant uterus during a single selected 2 hour period from an entire 3 months of gestational life, under the artificial conditions set up for recording uterine motility.

We think it significant, however, that there is a marked similarity between the two types of contraction patterns we have found in these patients and the two types of motility curves as demonstrated by several workers[34, 48-50] and ourselves[51] in the normal menstrual cycle (one pattern found in the proliferative

Fig. 5.—Cycle day 9. Proliferative phase pattern.
Fig. 6.—Cycle day 22. Secretory phase pattern.

phase and one pattern characteristically found in the secretory phase) (Figs. 5 and 6. Compare Figs. 3 and 4 with Figs. 5 and 6). Since the types of contractions in a normal menstrual cycle are thought to be due to estrogen (for the proliferative pattern) and to progesterone (for the secretory pattern), it seems logical to assume that the particular contractility pattern exhibited by a patient pregnant in the second trimester reflects a predominance of either estrogen or progesterone in the blood, depending on which type of pattern is found. It might also be theorized that cases which showed no uterine motility had a predominance of neither estrogen nor progesterone, but a neutralizing balance between the two. Unfortunately, no facilities were available for measuring serum or urine estrogen or progesterone values in these patients to confirm or negate these conclusions. Studies correlating urinary estrogen-pregnandiol excretion with uterine motility in the last trimester have been reported recently[52, 53]; however, until more satisfactory laboratory methods for determinations of ovarian steriod analyses are introduced, it will remain difficult to draw valid conclusions.

Moreover, careful perusal of the past gestational histories of each patient failed to disclose any convincing evidence that the presence of an "estrogenic" or "progesteronic" contractility pattern, or even a lack of any motility in this pregnancy, was related directly or indirectly to sterility, threatened or actual miscarriages, habitual abortion, premature labor, or abnormal labor in previous pregnancies.

It is our hope that the findings which we have presented and the conclusions which we have discussed will be of assistance in the increase of fetal salvage, and aid in the ultimate solutions of the perplexing obstetrical problems, the key to which is complete understanding of the physiology of the pregnant uterus.

Summary

1. The tokometric method of intrauterine carbon receptors has been used for the study of myometrial motility in 55 women pregnant in the tenth to the twenty-fourth week.

2. Uterine contractility was observed in 41 (75 per cent) of the patients and was in the form of one of two definitive patterns.

3. There was no evident uterine motility in 14 women (25 per cent).

4. Presence or absence of myometrial activity was not related to the patients' ages, parity, or duration of pregnancy, nor was there any discernible correlation with gestational histories of threatened, spontaneous, habitual, or missed abortions, premature labor, or abnormal labor.

5. Because of the remarkable similarity between the two observed motility patterns and those two contractility patterns known for the proliferative and secretory phases of the normal cycle, it is suggested that the type of myometrial activity in pregnancy depends on the dominance of either estrogen or progesterone.

6. The relationship of these findings to previous studies in animals and humans has been presented and their possible significance discussed.

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PRELIMINARY REPORT ON THE USE OF RELAXIN IN THE MANAGEMENT OF THREATENED PREMATURE LABOR

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RECENTLY a hormonal substance known as relaxin* has been made available for clinical trial. Although described by Hisaw[4] years ago, the safety of this preparation was not demonstrated until 1954 by Perkoff and others.[7] Previous reports have dealt with relaxin's chemical composition, properties, and its activity in animal experimentation.[5] It is a protein derivative of low molecular weight and is capable of inhibiting spontaneous or oxytocin-induced contractions of mouse uterine tissue in vitro. An important clue as to its activity in the human being was the demonstration by Zarrow and others[8] that this is a hormone of pregnancy. With the advent of a nontoxic commercial preparation, a new therapeutic approach in the management of threatened premature labor became available.

The first investigators to use this hormone for the management of this problem were Abramson and Reid.[1] They administered relaxin in various dosages to 5 patients in threatened premature labor. In all 5 instances they were able to control the uterine contractions and allow the patients to retain their gestations until 36 weeks or longer. Unfortunately, these workers did not determine the consistency, dilatation, or effacement of the cervix in all of their patients, but their encouraging preliminary report gave impetus for further trial and evaluation of relaxin in the management of threatened premature labor.

There are diverse etiologies which may excite premature labor and these add complexities to the problem. Only 28.0 per cent of all premature labors were found to be spontaneous at the Harper Hospital.[6] Premature rupture of the membranes instigated labor in 31.0 per cent of the cases while placental pathology such as premature separation and placenta previa were responsible for 12.0 per cent. Multiple pregnancy and toxemic states were the initiating factors in the remainder of the series. Other reports confirm the fact that slightly less than one-third of all premature labors are spontaneous in origin.[2] The precipitating cause of any given labor may remain obscure until delivery is completed. This primarily applies to cases with antepartum bleeding. It is also apparent that in certain toxemic states prolongation of

*Releasin, Warner-Chilcott Laboratories, to whom the authors are indebted for the material used in this study.

the gestation may prove harmful to the mother. If the efficacy of this preparation is to be determined it is imperative that the hormone be administered only in a controlled manner to alternate patients admitted to the hospital with threatened premature labor. For these reasons strict qualifications had to be made for the patients included in the present study.

Methods

The following criteria were established for selection of the patients to be included in this study.

1. The patient must be in the twenty-fourth to thirty-fourth week of gestation as determined by her estimated date of confinement. Patients of later gestation were excluded from the series in order to avoid the increased possibility of patients in false labor entering the study group. More important is the fact that in the earlier gestations the fetal morbidity and mortality are very high and, hence, deserving of improved management.

2. Uterine contractions must be established at intervals of every 10 minutes or less as judged by two competent observers, one of whom was not involved in conducting the study.

3. By vaginal examination the cervix should be not more than 2 cm. dilated. Effacement of the cervix did not contraindicate inclusion of the patient in the study.

4. Patients with other complications which would contraindicate prolonging the gestation, such as antepartum bleeding, toxemic states, or evidence of infection, were not acceptable. If mild bleeding or evidence of infection, such as amnionitis, pyelitis, etc., developed after the patient was admitted to the study group, therapy was continued if it was thought to be in the patient's best interest.

5. Patients with ruptured membranes were included in this series if the other qualifications were fulfilled.

Patients who met these criteria were selected and placed alternately in study and control groups. A concerted attempt was made to avoid bias in selecting from the private and ward services. In one instance only did the alternation of groups fail when one investigator was unaware of the sequence of assignment. The present series consists of 15 study and 15 control patients so selected.

TABLE I. SAMPLING VARIATIONS

	STUDY		CONTROL	
Ward patients	1	7%	8	53%
31-34 weeks' gestation	7	47%	11	73%
Premature rupture of membrane	7	47%	11	73%

In spite of the concerted effort to avoid bias in selection and alternation of the patients for the study and control groups, certain sampling variations did occur. This is not unexpected in dealing with such a limited series of cases. These sampling variations are listed in Table I. The larger number of patients with less advanced gestations in the study group makes the results slightly more impressive, while the greater number of patients with ruptured membrances in the control group decidedly decreases the significance of the control data. The increased number of ward service patients in the control group is also an important factor, since these patients must be considered to have a different socioeconomic and nutritional background.

The patients in the study group were treated with both intravenous and intramuscular relaxin until either the labor had been controlled or delivery became imminent. Therapy usually was initiated with a dilute intravenous infusion which was administered at a rapid rate (1,000 c.c. per 2 hours). The amount of relaxin given in the initial infusion varied from 50 to 200 mg. depending upon the frequency and quality of the contractions. If the uterine contractions were altered, repeat infusions were administered as indicated. Once the threatened labor appeared to be under control, small maintenance doses of 20 to 40 mg. were given intramuscularly at periodic intervals for the next 48 to 72 hours. In one instance a patient returned in premature labor because of premature rupture of membranes. The premature labor was treated with relaxin successfully for the second time. Total dosage in this series went as high as 800 mg. During relaxin therapy the patients were allowed to have 50 mg. of Demerol at 2 hour intervals for analgesia if necessary.

The patients in the control group received no relaxin but were given innumerable hormone and analgesic agents in various amounts at the discretion of the attending physician. Patients in either group with ruptured membranes received prophylactic penicillin and streptomycin therapy at regular intervals.

Clinical Response

All of the patients who received relaxin therapy demonstrated distinct alterations of the uterine contractions. Despite the modality which instituted the labor, decreased frequency and regularity of contractions could be induced by the drug. It is unfortunate that in most instances these changes were only temporary. In most of the cases some alteration in the frequency of contractions was noted in approximately 15 minutes. The action of the drug appeared cumulative in those who did respond completely, and within 2 hours their contractions became much weaker and more infrequent. At the end of 3 or 4 hours only an occasional mild contraction could be distinguished and these were controlled with periodic intramuscular relaxin therapy.

Those patients who did proceed to premature delivery also demonstrated some degree of uterine response to relaxin. This occurred within 15 minutes usually and was manifested by moderate alterations in uterine contractility. Unfortunately, this response was temporary, lasting only an hour or two. Contractions would then resume with increased regularity and tonicity. These labors were usually terminated in a tumultuous manner and were totally unresponsive to further relaxin therapy. In such cases some pathology related to premature labor was eventually detected.

Results

Table II shows the results obtained in attempting to halt 15 cases of premature labor with relaxin in comparison to the use of various narcotics, sedatives, and hormones in 15 control cases. The over-all survival rate was about the same in each group, which seems discouraging at first glance. There is a significant difference in the two groups, however, when one realizes that the average weeks' gestation in the study group was 30 in comparison to 31 for the control group; the gestation was prolonged one week or more in 8 cases (53 per cent) of the study group in comparison to one (7 per cent) of the controls; and the average weight of the babies from the study group was 245 grams more than the average of the controls. The delay period in the

8 study cases which were prolonged varied from one to 11½ weeks with an average of 5 weeks per case. Four gestations in the study group were prolonged until the babies attained a weight over 2,500 grams while only 2 were found in the control group. One of the latter patients was delivered within 24 hours after admission and the baby weighed 2,560 grams. This case probably represents an error in estimating the expected date of confinement.

TABLE II. COMPARISON OF TREATED AND CONTROL CASES

	STUDY		CONTROL	
Number of cases	15		15	
Living babies	10	66%	9	60%
Average birth weight	1,939 grams		1,695 grams	
Average weeks' gestation at onset of labor	30		31	
Gestations prolonged more than one week	8	53%	1	7%
Infants 2,500 grams or more	4		2	
Stillbirths	1		1	

Table III shows the influence of premature rupture of the membranes. The gestations were prolonged more than one week in 3 of the 7 study cases; however, 2 of these patients developed intrapartum fevers and both of these babies died. Labor was not delayed in any of the control patients. It appears significant even in this small series that prolongation of the gestation with frank rupture of the membranes may increase the fetal risk.

TABLE III. PREMATURE RUPTURE OF MEMBRANES

	STUDY		CONTROL	
Number of cases	7		11	
Living babies	4	57%	7	63%
Gestations prolonged more than one week	3	43%	0	0%
Stillbirths	1		1	
Intrapartum fever	2		0	

Table IV shows the cases with evidence of placental pathology detected either before or after delivery. It will be noted that in none of these cases could labor be altered with or without therapy.

TABLE IV. PLACENTAL PATHOLOGY

	STUDY		CONTROL	
Number of cases	3		3	
Living babies	2	66%	1	33%
Gestations prolonged more than one week	0	0%	0	0%

In Table V the 8 cases with maternal complications are listed. These included pyelonephritis, amnionitis, intrapartum fever of unknown etiology, and rupture of an ovarian cyst (endometriosis). Although gestation was prolonged more than one week in 3 patients in the study group, only a single newborn infant survived as in the controls.

TABLE V. MATERNAL COMPLICATIONS

	STUDY		CONTROL	
Number of cases	5		3	
Living babies	1	20%	1	33%
Gestations prolonged more than one week	3	60%	1	33%

In the complete series of 30 cases there were only 6 which were completely free of the various complications which have been described. These

6 cases are summarized in Table VI. Unfortunately only one of these patients was a control. The 5 patients who received relaxin therapy had gestations prolonged over one week and all of these resulted in living babies.

TABLE VI. UNCOMPLICATED PREMATURE LABOR

	STUDY		CONTROL	
Cases	5		1	
Living babies	5	100%	0	0%
Gestations prolonged more than one week	5	100%	0	0%

Comment

From these observations it appears that relaxin does have a definite effect on uterine contractions initiated prematurely. Eichner and others[3] have demonstrated recently that this agent also can influence the uterus contracting at term. In premature labor, however, the activity of relaxin will not be sustained if such complicating factors as placental pathology, amnionitis, and severe intrapartum fever are present. Although the gestation may be temporarily prolonged in such cases, the final neonatal survival rate does not appear to be influenced. In the true idiopathic premature labor, however, relaxin does seem to inhibit uterine contractions and allow the gestation to continue without apparent deleterious effects on the mother or child.

Summary

Thirty patients admitted to the hospital in threatened premature labor were studied. Alternate patients were treated with the hormone relaxin. The cases were analyzed as to total fetal survival, birth weight, influence of premature rupture of the membranes, placental pathology, and maternal complications.

Conclusions

1. Relaxin does have an inhibiting effect on premature uterine contractions.

2. Relaxin appears to be contraindicated if the membranes have ruptured prematurely.

3. Relaxin appears to be of little use in the presence of placental pathology or severe maternal complications.

4. Although the control material in uncomplicated cases was insufficient, relaxin appears to have a definite place in arresting premature uterine contractions in these cases.

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SYPHILIS IN PREGNANCY, WITH SPECIAL EMPHASIS ON SEROLOGIC PROBLEM CASES

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THE diagnosis and treatment of syphilis in pregnancy are the same as the diagnosis and treatment of syphilis in any patient. In pregnancy, though, they are doubly important because we want to cure the pregnant woman and prevent syphilis in the baby.

The earlier in pregnancy the diagnosis of syphilis has been established and antisyphilitic treatment given the better the prognosis for the pregnant woman and especially for the unborn baby. Syphilitic infection of the fetus in utero usually does not take place before the fifth month of pregnancy.[1, a] That is why we usually do not find *Treponema pallidum* in fetuses of up to 5 months but numerous Treponema in older fetuses; that is why the incidence of abortions in syphilitic mothers is not higher than in the nonsyphilitic, but the incidence of stillbirths is eight times as high in syphilitic as in nonsyphilitic patients; and, most important, that is why we get healthy babies if we treat the mother before the fifth month of pregnancy, and may get syphilitic babies if we treat the mother after the fifth month of pregnancy. The incidence of prenatal syphilis is the higher and the involvement the more severe the later in pregnancy we treat the syphilitic mother, but later is still better than never!

From the pathologist's point of view, one possible explanation for this peculiar propensity of syphilitic infection of fetuses to occur after the fifth month of pregnancy and not before that time is the following: The maternal and the fetal circulations are separate. The chorionic villi of the placenta are bathed in a pool of maternal blood. The tissues separating the maternal blood from the fetal blood consist of the endothelial cells of the fetal capillaries, the mesoderm that makes up the substance of the chorionic villi, and the epithelium covering the villi. This epithelium covering the villi consists of two layers: the inner cytotrophoblast and the outer syncytiotrophoblast. After the first trimester of pregnancy the cytotrophoblast gradually disappears. The trophoblast is specialized epithelium endowed with ability to destroy any tissue it comes in contact with.[1, b] The gradual thinning of this specialized epithelium might have something to do with the fact that syphilitic infection of the fetus takes place in the fifth month or thereafter, usually not before.

The diagnosis is made upon a complete history, physical examination, and laboratory procedures. When both the history and the physical examination are completely negative for syphilis, we have to rely on the serologic tests. Forty-two states have laws requiring a serologic test for syphilis as soon as the diagnosis of pregnancy has been established. Comparison of the standard serologic tests for syphilis (STS) with the highly specific Treponema Pallidum Immobilization tests (TPI) performed in "serologic problem cases" forms the nucleus of this paper. To qualify as a "serologic problem case," three criteria have to be fulfilled: (1) the history for syphilis has to be negative; (2) physical examination for syphilis has to be negative; and (3) the STS (standard serologic test for syphilis) has to be equivocal, i.e., not definitely negative, nor definitely positive; e.g., Kolmer negative, Kahn doubtful; or VDRL reactive;* Kolmer ±0000, etc.

The problem in "serologic problem cases" is whether they represent syphilis or rather a biologically false response. In order to determine this, we performed on these patients TPI tests. The TPI test is highly specific. We do not mean to say that a positive TPI test always means syphilis, and a negative TPI test always means no syphilis. There are exceptions, e.g.: (a) In many cases of primary syphilis and in some cases of secondary syphilis where *Treponema pallidum* can easily be demonstrated under the dark-field microscope the TPI test is negative. This is no contradiction, though, and does not deduct from the value of the TPI test. The TPI test is based on the presence of specific *Treponema pallidum* immobilizing antibodies in the serum.[2] To manufacture these specific antibodies takes time; it takes longer time than the incubation period of syphilis is; generally it takes longer than it takes to manufacture the reagin antibodies which are responsible for the positive standard serologic tests. (b) Another "exception" is exemplified by the healthy baby of a syphilitic mother who prior to pregnancy or early in pregnancy was adequately treated for syphilis but whose TPI test stays positive and whose TPI antibodies were passively transferred to the fetus.[3] The infant is not infected with syphilis, therefore it will not manufacture its own TPI antibodies; but temporarily—usually for the first six months—will give a positive TPI test in the absence of syphilis because its serum contains the TPI antibodies passively transferred from the mother. (c) The TPI test is positive not only in syphilis but also in other treponematoses: yaws, bejel, pinta, etc. But these conditions are in this country rare indeed, and, even though they are not identical with syphilis, both diagnosis and treatment of these conditions are very similar to those of syphilis. Despite these exceptions the TPI test is very valuable, highly specific, and, if interpreted intelligently, will clarify practically all of the serologic problem cases.

Some authors[4] have stated that pregnancy is one of the conditions that may cause biologically false positive (BFP) reactions in the standard serologic

*VDRL means Venereal Disease Research Laboratory serologic test. Recently laboratories designate the results of the serologic tests as "Reactive" (R), "weakly reactive" (WR), "non-reactive" (NR). These terms correspond to the previous designations: positive, doubtful, negative.

tests for syphilis. This belief has never been *proved.* Most of the series reported contain pregnant and nonpregnant patients and both groups had TPI tests. But there was a difference in criteria in selecting pregnant and nonpregnant patients for the test. During pregnancy, the slightest suspicion (e.g., a single doubtful serologic report) was considered sufficient reason to perform the TPI test without delay; not so in the nonpregnant group. Since the selection of patients for the TPI test was not based on the same criteria in the pregnant and in the nonpregnant groups, these two groups are not comparable without adjustment.

The belief that pregnancy causes biologically false positive reactions is dangerous because it lulls us into a false sense of security. Any mistake we make on that account is doubly sad; we fail to cure the syphilitic pregnant woman and we fail to prevent prenatal syphilis in the baby.

Whether pregnancy causes biologically false positive reactions can be scientifically proved or disproved by two methods: (1) comparing statistically large enough series of TPI tests in pregnancies and similar series in males and nonpregnant women, using *exactly the same criteria* in selecting patients for TPI tests; (2) taking a statistically large enough series of women in the childbearing age who have never been pregnant and following them for a longer period (e.g., five years) with monthly physical examinations and monthly serologic tests. During the five-year period a number of these women will become pregnant. Through the monthly follow-up it will become evident: (a) whether the STS changes during pregnancy from negative to doubtful or positive; (b) if it changes, whether it is due to syphilis or to biologically false positive reactions; (c) if there are biologic false positive reactions, at what stage or in which month(s) of pregnancy these BFP reactions occur; (d) how long they persist; and (e) at what time in relation to pregnancy or delivery they disappear.

Material and Method

The following is a preliminary report on the first method. The project started in March, 1956. From then on, every patient who qualified as a "serologic problem case" was enrolled in the program, regardless of whether the patient was male or female, pregnant or nonpregnant, young or old. The only question in selection of the patients was whether or not they satisfied the three criteria of "serologic problem cases": (1) history for syphilis negative; (2) physical examination for syphilis negative; and (3) standard STS equivocal, not definitely negative nor definitely positive.

Between March, 1956, and October, 1956, 100 serologic problem cases were studied. The study included history, physical examination, standard STS (most of them had several different serologic tests, many repeatedly), and TPI test (some repeatedly).

The group was composed of 41 males and 59 females. Forty of the males were Negro and one white. There were 51 Negro women, 7 white, 3 of whom were Mexicans, and 1 American Indian. Among the 28 pregnant women, 24 were Negro, 3 white (2 of them Mexicans), and 1 American Indian.

The ages of the patients varied between 15 and 61 years, with a mean of 38 and an average of 31.37 years. The ages of the pregnant women varied between 18 and 38 with a mean of 28 and an average of 26.21 years.

Results

A positive TPI test indicates syphilis; a negative TPI test indicates a biologic false positive reaction. The TPI test was negative in 63 patients and positive in 37. It was negative in 32 males (78.05 per cent), and positive in 9 (21.95 per cent); negative in 31 females (52.54 per cent), and positive in 28 (47.46 per cent); negative in 12 of the pregnant women (42.86 per cent), and positive in 16 (57.14 per cent); negative in 19 of the nonpregnant women (61.29 per cent), and positive in 12 (38.71 per cent).

The group of all nonpregnant patients (males and nonpregnant females together) consisted of 72 individuals. The TPI test was negative in 51 (70.83 per cent), and positive in 21 (29.17 per cent).

The incidence of BFP reactors in our total group and in the different subgroupings is presented in Table I.

If pregnancy as such would cause biologic false positive reactions it would be expected that the incidence of BFP reactors in the group of pregnant patients would be higher than in the total group and especially higher than in the group consisting of all nonpregnant patients. This is not the case. In fact, the group of *pregnant patients shows* the *lowest incidence of biologic false positive reactions* of all the groups: it is lower by 20 per cent than in the total group; and lower by 28 per cent than in the group containing all nonpregnant patients.

TABLE I. INCIDENCE OF BFP REACTORS

NO. OF PATIENTS IN EACH GROUP		NO. OF BFP REACTORS	%
Total No. of patients	100	63	63
Males	41	32	78
Females	59	31	53
Pregnant females	28	12	43
Nonpregnant females	31	19	61
All nonpregnant patients	72	51	71

The group is statistically small; but every individual was selected on *exactly* the same criteria and so the cases are scientifically comparable. Further studies with larger groups and with both methods previously outlined must continue. But the observations so far do not support the assumption that pregnancy itself causes biologic false positive reactions. In this series the opposite seems to be true.

The serologic studies (both standard STS and TPI tests) of all 28 pregnant patients are reported in detail in Table II.

Case 20 had a just weakly reactive VDRL test; at the same time the Kolmer test was negative. On repeat testing 9 days later all three standard serologic tests (Kahn, Kolmer, VDRL) were negative. Still the TPI test was positive!

Case 10 was similar. On the first testing just the VDRL was reactive, undiluted only; weakly reactive in 1:2 dilution; nonreactive in higher dilutions. At the same time both Kahn and Kolmer tests were negative. On repeat testing three weeks later and again three months later all three standard tests (Kahn, Kolmer, VDRL) were negative. Still the TPI test was positive!

Table II contains a number of cases (Nos. 2, 3, 4, 16, 17, 22, 23, 25, 27) where a battery of standard serologic tests was performed; only one STS was weakly reactive (not even positive), at the same time the other serologic test(s) were negative; still the TPI test was positive. Therefore, we must not carelessly or lightheartedly disregard even a single doubtful or weakly reactive serologic report; all such cases have to be investigated.

Observations

Since 1951 and independently of the present study we performed the TPI test on 670 patients, all of whom presented diagnostic problem cases in regard to syphilis. In some of these cases the TPI test was performed repeatedly. Here are briefly a few salient points from our observation:

1. Whenever a TPI test that first was reported negative was repeated, the report always came back again negative.
2. Whenever a TPI test that first was reported positive, was repeated, the report always came back again positive. In regard to these points, it is to be noted that the TPI laboratory had no way of identifying the patient, it could not just "copy" the previous report, nor could it be influenced by the result of the first TPI test.
3. In some cases the result of the first TPI test is equivocal and the laboratory report reads "doubtful" or "inconclusive" or "invalid" or "hemolyzed" or "fat particles in the serum," etc. In such cases the TPI test has to be repeated, in rare instances more than once, until an unequivocal negative or an unequivocal positive report is obtained. In our group of 100 serologic problem cases this happened in 7 patients. On repeat testing 2 of these cases turned out to be negative, and 5 positive. In 5 cases it took one repeat testing to get a conclusive report; in one case the TPI test had to be repeated twice and in one case (Case 16 in Table II) it took altogether four TPI tests until finally an unequivocal report was obtained. Many of the "invalid" reports can be avoided by following the instructions enclosed in the TPI kit: the patient must not have had penicillin or other antibiotics within the last ten days; the sterile syringe furnished in the TPI kit must be used, etc. Many of the "inconclusive" results can be avoided by immediately stoppering the tubes as soon as the blood is drawn or by using paraffin-coated cork stoppers.[5]
4. The more serologic problem cases we study, the more convinced we become that the outcome of the TPI test cannot be rightly predicted from the standard serologic tests, not even if a whole battery of different standard serologic tests is performed, and repeated on several occasions. In true serologic problem cases we can only guess whether the TPI test will be negative or positive; and our guesses will probably be right 50 per cent of the time, in the same proportion as anybody's guess. In serologic problem cases the TPI test cannot be predicted; it should not be guessed; it should be performed.

In syphilis the TPI test may stay positive for a long time, even after adequate treatment. Especially if treatment is given not in early syphilis but in late syphilis, the TPI test usually remains positive for many years, probably for life. Therefore, a positive TPI test does not indicate activity of syphilis; it does not indicate need for further treatment or for retreatment; but it does indicate syphilis—past or present.

Treatment

The TPI test should be used in serologic problem cases. If the patient is in the first half of pregnancy, we take a TPI test and the further management depends on the outcome of that test. If the patient is first seen in the second half of pregnancy, we take a TPI test and start antisyphilitic treatment immediately, without waiting for the report of the test, which may take 2 to 3 weeks. Somebody may ask: "Why take the TPI test if you give treatment anyway?" The answer is this: There is no sound medical practice without correct diagnosis. The pregnant patient is entitled to know whether or not she has syphilis. This has not only moral and social implications, and not only academic value. There is much more to syphilis than giving a few penicillin

TABLE II. SEROLOGIC REPORTS (STANDARD STS AND TPI) OF 28 PREGNANT PATIENTS

NO.	PREGNANCY	STS	TPI
1	Due date 9/25/56	4/11/56 Kahn WR; VDRL WR; Kolmer 00000 5/18/56 Kahn negative; VDRL negative; Kolmer 00000	Negative 8/2/56
2	Due date 7/27/56	3/15/56 Kahn negative; VDRL WR; Kolmer 00000	Positive 4/2/56
3	Due date 9/6/56	3/5/56 Kahn negative; VDRL WR; Kolmer 00000 5/29/56 VDRL negative 6/19/56 Kahn negative; VDRL negative 7/24/56 VDRL WR; Kolmer 00000	Positive 3/15/56
4	Due date 5/25/56	11/3/55 Kahn negative; VDRL WR; Kolmer 00000 12/5/55 VDRL WR; Kolmer 00000 1/17/56 Same as on 11/3/55	Positive 3/20/56
5	Due date 3/22/56	1/24/56 Kahn WR; VDRL negative 2/9/56 Kahn negative; VDRL negative; Kolmer 00000 2/16/56 Kahn WR; VDRL negative; Kolmer 00000 2/28/56 Kahn positive; VDRL negative; Kolmer 00000	Negative 5/1/56
6	Stillbirth 12/16/55	10/15/55 Kahn doubtful; Wassermann doubtful 12/13/55 Kahn doubtful; Wassermann doubtful 2/10/56 Kahn positive; VDRL R.R. R.R.WR.N; Kolmer ±0000	Positive 8/13/56
7	Due date 7/12/56	12/19/55 Kahn positive; VDRL negative; Kolmer anticomplementary 2/23/56 Kahn positive; VDRL negative; Kolmer 00000	Negative 3/30/56
8	Delivery 6/1/56	1/15/56 Kahn negative; Wassermann doubtful 3/2/56 Kahn negative; Kolmer positive 3/7/56 Kahn negative; VDRL negative; Kolmer 00000 4/23/56 Kahn negative; VDRL negative; Kolmer 44000	Positive 5/10/56
9	Due date 9/8/56	3/8/56 Kahn negative; VDRL WR; Kolmer 00000 3/22/56 Kahn negative; VDRL negative; Kolmer 00000 4/19/56 Same as on 3/22/56	Negative 7/17/56
10	Due date 8/22/56	3/15/56 Kahn negative; VDRL R.WR.N; Kolmer 00000 4/5/56 Kahn negative; VDRL negative; Kolmer 00000 6/19/56 VDRL negative; Kolmer 00000	Positive 4/5/56
11	Abortion 3/8/56	3/6/56 Kahn doubtful; Wassermann negative	Negative 4/20/56
12	Due date 4/16/56	3/16/56 Kahn negative; Wassermann positive 5/1/56 Kahn negative; VDRL negative; Kolmer 20000	Negative 5/7/56

TABLE II.—CONT'D

NO.	PREGNANCY	STS	TPI
13	Cesarean section 3/26/56	3/16/56 Kahn doubtful; Wassermann doubtful 3/22/56 Kahn negative; Wassermann doubtful 4/30/56 Kahn negative; VDRL R.N; Kolmer ±0000	Positive 5/9/56
14	Curettage 4/16/56	4/16/56 Kahn negative; Wassermann doubtful 5/16/56 Kahn negative; VDRL negative; Kolmer ±0000 5/25/56 Same as on 5/16/56	Negative 6/29/56
15	Abortion 4/20/56	4/20/56 Kahn doubtful; Wassermann doubtful 5/24/56 Kahn negative; VDRL negative; Kolmer 00000	Negative 6/6/56
16	Delivery 7/25/56	5/2/56 Kahn negative; VDRL WR; Kolmer 00000	1. Doubtful 5/29/56 2. Inconclusive 6/21/56 3. Invalid 7/25/56 4. Positive 8/10/56
17	Due date 9/27/56	4/18/56 Kahn negative; VDRL negative; Kolmer ±0000 5/31/56 Same as on 4/18/56	Positive 7/11/56
18	Delivery 3/23/56	3/24/56 Kolmer negative; Kline positive 6/14/56 Kahn negative; VDRL negative; Kolmer 00000	1. "Fat particles" 8/29/56 2. Positive 9/28/56
19	Delivery 5/22/56	5/22/56 Kahn negative; VDRL WR 5/25/56 Kahn negative; VDRL WR	Negative 6/20/56
20	Due date 12/10/56	6/27/56 VDRL WR; Kolmer 00000 7/6/56 Kahn negative; VDRL negative; Kolmer 00000	1. "Hemolyzed" 8/8/56 2. Positive 9/6/56
21	Abortion 7/20/56	7/20/56 Kahn positive; VDRL positive; Wassermann negative	Negative 8/20/56
22	Delivery 6/15/56	6/15/56 Kahn negative; Wassermann doubtful 8/14/56 VDRL negative	Positive 9/4/56
23	Ectopic pregnancy 6/19/56	6/19/56 Kahn negative; Wassermann doubtful	Positive 8/21/56
24	Delivery 9/6/56	7/21/56 Kolmer negative; Kline positive	Positive 8/24/56
25	Due date 3/23/57	9/17/56 Kahn negative; VDRL WR; Kolmer 00000	Positive 9/27/56
26	Last menstrual period 7/24/56	8/3/56 Cardiolipin 2 plus 8/8/56 Kahn negative; VDRL negative; Kolmer 00000	Negative 9/27/56
27	Due date 1/4/57	9/13/56 Kahn negative; VDRL negative; Kolmer ±0000	Positive 9/27/56
28	Ectopic pregnancy 11/2/55	12/7/55 Kahn WR; VDRL negative; Kolmer 00000	Negative 10/2/56

injections. If the patient has syphilis, there has to be, in addition to adequate treatment, adequate posttreatment follow-up, including spinal tap and cardiovascular fluoroscopy at the proper times, and the baby has to be followed up.

Penicillin treatment given on the sole basis of one positive or doubtful standard serologic test for syphilis without further investigation is to be condemned. Moreover, a patient who already has had adequate treatment for syphilis does not need further treatment or retreatment during pregnancy or during repeated pregnancies; not even if she is serofast, i.e., not even if the standard STS stays positive or if the TPI test stays positive or if both stay positive. We do not treat for pregnancy but for syphilis; and for syphilis she has already had adequate treatment. Of course, if there is any indication of relapse (serologic or clinical) or of reinfection, immediate treatment is indicated. Serologic relapse, in contrast to serofastness, is illustrated by the following example:

Serofastness:

Kolmer in May, 1949: 44444.
Adequate treatment given in June, 1949.
All subsequent Kolmer tests (in 1950, in 1952, in 1955, in 1956): 44444.

Serologic relapse:

Kolmer in May, 1949: 44444.
Treatment given in June, 1949.
Kolmer in December, 1949: 43210.
Kolmer in 1950, in 1952, in 1955, all: 00000.
Kolmer in 1956: 44430.

"Acute" biologically false positive reactions occur in a number of conditions (e.g., malaria, infectious mononucleosis, recent vaccination, pneumonia, etc.); these acute BFP reactions disappear a few weeks or a few months after recovery.

"Chronic" biologically false positive reaction (i.e., persistent reaction) may precede systemic lupus erythematosus, sometimes for years.

Biologically false positive reactions may even occur at times in "normal" persons, or—more properly worded—in absence of any conditions usually responsible for BFP reactions. But we have to start from a base line, and the base line should be that a normal person will have negative STS every time it is performed. If it is not negative, it should be investigated further. An excellent method for differentiation between true syphilitic and biologically false positive STS is the TPI test.

The still newer *Treponema pallidum* tests, like the TPA (Treponema pallidum agglutination) test, TPCF (Treponema Pallidum Complement Fixation) test, TPIA (Treponema Pallidum Immune Adherence) test, etc., have not been evaluated enough, have not been generally accepted as yet, and are more or less in the experimental stage. Their chief value lies in the fact that while the TPI test—using live, virulent, actively motile *Treponema pallidum*—is a highly complex, time-consuming procedure, these other tests—using killed *Treponema pallidum* that can be kept in the refrigerator for months—should give the same answer as the TPI test but with a much simpler, easier, and cheaper laboratory procedure.[7]

Summary

Syphilis in pregnancy is doubly important because it affects the life and welfare of both mother and baby. The criteria for serologic problem cases are defined. The TPI test is an excellent method of differentiating between true syphilitic and biologically false positive standard serologic tests for syphilis. The assumption that pregnancy causes biologically false positive reactions has

never been proved. The analysis of 100 serologic problem cases, including 28 in pregnant patients, does not seem to support this assumption. Indications for treatment are briefly outlined.

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THE MOON AND THE BIRTH RATE

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YOU look out of your window and you notice that round, bright-shining full moon. How often has the thought struck you: "The delivery room is going to be busy tonight!" Is this a superstition, is it an old belief ready to be discarded, or is there any truth in it?

In the earliest beginning of medicine, the moon's periodic birth, growth, decline, and death were considered to affect human undertakings as well as ailments.[10] The influence of the stars, especially on birth and on the newborn infant's future, is still recognized today in astrology, but the moon as a factor in medicine disappeared in the eighteenth century.[14] Its influence on pregnancy and delivery, however, remain a popular superstition to this day. Publications from India, Europe, and South America show a world-wide spread of this belief.[1-4, 6-8]

Only in 1938 the first scientific report was published. The author, Günther,[9] came to the conclusion that more deliveries occur seven to nine days after the full or new moon. He found that true on the German coast of the North Sea, and he was undecided whether his findings were due to lunar influence directly or connected with the tides. He mentioned the studies by Grabley[5] concerning radon concentration in the air as a possible factor, which increases at the time of the full moon and decreases at the new moon.

In 1950 Hosemann[11, 21] showed with tables and diagrams that the phases of the moon have no connection whatsoever with the daily birth rate. The same year the first and only mention in the American medical literature was made by Schnurman.[13] He found that in a 5-year period with 2,691 births, a lunar effect was noticeable in 40 months, or in 66.7 per cent. He considered the lunar influence effective when the largest number of deliveries occurred at the time of the full moon or 24 hours before or after.

Our Report

No definite proof for or against this theory concerning a large number of deliveries had ever been obtained in this country. In this article we investigate the possibility of a relation between the moon's phases and deliveries.

The study is based upon the deliveries during the last 10 years at the George F. Geisinger Memorial Hospital in Danville, Pa., i.e., from Jan. 1, 1946, to Dec. 31, 1955. We excluded from our series all cesarean sections, since the pregnancies in those cases are terminated by our intervention, according to our judgment. Only patients who went into labor spontaneously and were delivered vaginally are considered.

During this time there were 9,551 vaginal deliveries. This is a daily average of 2.62 deliveries. The average daily birth rate was at its lowest in 1946 with 2.22 and at its highest in 1953 with 2.81.

We assumed that deliveries at the full moon are more frequent. As an arbitrary number we set up 6, which is more than double the average daily birth rate. During the 10 years considered, the rate of 6 or more was reached thirteen times, seven times at full moon and six times at new moon. A total of 324 babies were born at the full moon against 334 at the new moon. The details are given in Table I. These figures show a slight tendency against our assumption but are not enough evidence by far to prove or disprove it.

TABLE I

YEAR	DAYS OF FULL MOON	BIRTHS AT FULL MOON	DAYS OF NEW MOON	BIRTHS AT NEW MOON	OUTNUMBERING PHASE OF MOON	TOTAL	AVERAGE
1946	12	27	13	34	N*	61	2.44
1947	12	25	13	38	N	63	2.52
1948	12	33	13	36	N	69	2.76
1949	12	25	12	24	F†	49	2.04
1950	12	40	13	45	N	85	3.40
1951	13	25	12	37	N	62	2.48
1952	13	45	12	30	F	75	3.00
1953	13	30	12	32	N	62	2.58
1954	12	35	13	30	F	65	2.40
1955	13	39	12	28	F	67	2.64
Total	124	324	125	334	6N/4F	658	
		49.24%		50.76%	3:2	100%	

*New moon.
†Full moon.

Since a clear increase of deliveries at the full moon cannot be shown, we investigated other possibilities of periodicity. If the birth rate is high at the full moon, it logically should be low at the new moon. Table I shows that the deliveries at the new moon outnumber the deliveries at the full moon by 3 to 2.

If there is any truth to this old belief, the highest numbers of deliveries should fall in the time of the full moon or at least within 24 hours before or afterward. The highest number of births in any one day was 11. It occurred two days after the full moon. On two occasions we had 10 deliveries. Once it happened exactly halfway between the full and the new moon, the other time it occurred the day after the full moon. On two days 9 babies were born, once 7 days after the new moon and once 4 days before the new moon. That means that more babies are born close to the new moon than to the full moon.

According to our assumption, the average daily birth rate at the full moon plus that at the new moon should equal the over-all daily average. But this figure is very variable, as the table shows, ranging from 2.04 to 3.40.

With this study we have proved statistically that there is no reliable evidence of the moon's influence on the daily birth rate.

Conclusion

We felt like the gamblers at Monte Carlo who sit day after day at the roulette table, marking down the numbers hit by the roulette ball in their sequence, to figure out a sure system to win. There, as here, is no system or periodicity. It is high time to discard that superstition.

Summary

Based on 9,551 deliveries, we investigated the theory of lunar influence on the daily birth rate. No connection between the phases of the moon and the number of deliveries could be established.

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3,772 LABORS FOLLOWING RADIOGRAPHIC MENSURATION*

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FOR centuries it has been recognized that distortion of the bony pelvis could alter the course of labor, prevent vaginal birth of a living child, or totally prevent birth of any child of average size. On the other hand, modern knowledge of the bony pelvis is quite recent. It began in 1861 when Litzmann offered numerical standards for size of the inlet. In 1909 Williams produced criteria for the outlet. In 1936 Hanson offered measurements, obtained manually in nearly 4,000 women, for the midplane. Thus, mensuration of the bony pelvis is a relatively recent achievement of obstetrics.

Radiographic mensuration did not become established as standard procedure until about 10 years ago. Even today there are many obstetricians who believe that x-ray mensuration is superfluous and represents a needless expense. On the other hand, it is impossible to measure all essential pelvic diameters manually. There is no manual way to measure the transverse diameter of the inlet and, despite Hanson's ingenuity, manual measurement of the transverse diameter of the midplane is technically difficult for most of us.

It is not our purpose tonight to argue the relative merits and demerits of various methods of mensuration. In fact, we are not basically interested in *method* of measurement, conceding that any modern radiographic method of measuring, or estimating, pelvic diameters offers much greater accuracy than we can use in prognosticating the outcome of human birth. We are primarily interested in the *utilization* and *interpretation* of the gross data supplied by our colleagues in radiology.

There are five components of cephalopelvic disproportion: (1) size and shape of the bony pelvis, (2) force exerted by the uterus, (3) size of the fetal head, (4) moldability of the head, (5) presentation and position.

At least three of these cannot be ascertained until *after* the onset of labor. How absurd, therefore, it becomes in all cephalopelvic disproportion to try to reduce the situation to mathematical exactitude! We can measure the pelvis, we can estimate the size of the head, but attempts to anticipate the forces of labor are futile. I believe that the problem of cephalopelvic disproportion will remain in the realm of the art of obstetrics, rather than of its science.

*Presented at a joint meeting of the Chicago Gynecological Society and the Chicago Roentgen Society, April 20, 1956.

Our studies of the outcome of labor in relation to the internal diameters of the bony pelvis began in 1945 and culminate tonight with the presentation of data on nearly 4,000 labors with the internal diameters of the inlet and midplane known prior to the onset of labor. When these studies began we decided to employ the ultimate test of labor, namely, 2 hours of second stage with the membranes ruptured. Except in a very few instances where such a test would have been ridiculous, no interference before this stage was permitted in the first series of 935 women, reported in the year 1948. During this period, the total incidence of cesarean section for the entire service, for any reason whatsosever, fell to less than 0.6 per cent. Obviously, such stringent tests are not acceptable for routine clinical use. Today, we allow a certain number of hours of labor, seldom exceeding 12, in all cases of doubt. We believe we are testing, not the relation of head to pelvic size, but the *forces* of *labor*. In other words we are testing the character of uterine contractions. More and more we are coming to believe that successful vaginal birth in doubtful situations depends largely upon the driving force of the uterus.

During the course of our studies, it was inevitable that attention became focused on the midplane, despite the fact that it has been taught that contraction of a degree to cause dystocia occurred most often at the inlet, seldom at the outlet, and almost never in the terra incognita of the midpelvis. This teaching is not substantiated by our figures (Table I), since isolated midplane contraction was the most common type, occurring in 10.5 per cent of our patients. The relative incidence of isolated inlet contraction was 8.9, and of contraction of both planes, 6.3 per cent.

TABLE I. RELATIVE FREQUENCY OF PELVIC CONTRACTION (85 PER CENT OR LESS)

	PATIENTS	
	NO.	%
TOTAL	3,772	
Midplane only	398	10.5
Inlet only	336	8.9
Biplanar	238	6.3

At first we directed attention to all three recognized pelvic planes: inlet, mid, and outlet. It soon became apparent that the outlet could be ignored if we knew the internal measurements of the midplane. It is doubtful if outlet dystocia exists as a separate entity, unassociated with midplane contraction. This was evidenced in the first series of patients by the fact that the transverse diameter of the outlet was shorter than the transverse of the midplane in only 2 instances. Even in these 2 patients, the difference was negligible. Conversely, if the transverse diameter of the midplane is normal, it is virtually impossible for the transverse diameter of the outlet to be significantly contracted. We believe that a narrowed outlet represents only the reflection of a transverse midplane contraction.

Patients

Data are available on 3,772 labors following radiographic mensuration where the child weighed more than 1,500 grams. These patients were observed over a period of 11 years, and were not necessarily seen consecutively. In some instances, more than one labor occurred in the same patient. The women mostly were indigent and largely represented an underprivileged segment of the population. In all other respects they were an average clinic group.

Method

The graphic area method employed in this study is based upon two premises: (1) if the height and width, and thus the area, of a sufficient number of cross sections of a tortuous, curving, passageway are known, imaginative reconstruction of the passageway is facilitated. (2) Since the bony passageway which is the human pelvis is no more than 5 cm. high in front and about twice that posteriorly, two cross-sectional areas supply adequate information for all practical purposes. As mentioned before, we no longer estimate the capacity of the pelvic outlet and, in patients whose midplane dimensions are known, have experienced no unanticipated or untoward consequences.

The graphic area method may be briefly summarized. The internal anteroposterior and transverse diameters of each plane are multiplied together, giving an imaginary area. From the first group of patients we found the average area of the inlet to be 145 sq. cm. and of the midplane, 125. Each of these areas was arbitrarily designated as 100 per cent of capacity, and any given patient referred to the established average. Thus a patient, the product of whose inlet anteroposterior and transverse diameters is 130, is said to have 90 per cent of average inlet capacity (130 divided by 145).

From experience we found a sharp division point at 85 per cent of average capacity. Thus, we designate a pelvis as contracted when either or both planes are 85 per cent or less.

Results

There were 3 maternal deaths in the 2,800 women with normal pelves, 2 from eclampsia and one from a transfusion reaction. There was one death from cardiac arrest during cesarean section in the 972 women with contracted pelves.

Fifty-eight children in the normal-pelvis group and 19 in the contracted-pelvis group succumbed. When antenatal death and congenital anomalies incompatible with life were eliminated, the figures became 48 (1.7 per cent) for the normal and 14 (1.4 per cent) for the contracted pelvis group.

TABLE II. ESSENTIAL PELVIC MEASUREMENTS (AVERAGES IN CENTIMETERS)

	ACCEPTED STANDARDS	FIRST SERIES 935 PATIENTS	SECOND SERIES 3,772 PATIENTS
Inlet.—			
Anteroposterior	11.5	11.6	11.6
Transverse	13.0	12.5	12.2
PRODUCT	149.5	145.0	141.5
Midplane.—			
Anteroposterior	11.5	12.1	11.8
Transverse	10.5	10.3	10.3
PRODUCT	120.8	124.9	121.5
Posterior sagittal	5.0	4.6	4.3

The average pelvic measurements of the patients of our series are shown in Table II. Despite the small variations of inlet and midplane areas, we plan to retain the basic figures of 145 and 125. They are easy to remember and we believe that, because of the type of patients, standards based upon our series tend to be low. Also, data and clinical judgments are based upon these criteria. Moreover, a change of 5 sq. cm. in the standard produces a change of only 3 in the calculated percentage. This is barely significant in the management of the clinical course of labor, in view of the magnitude of the other variables of cephalopelvic disproportion.

The effect of pelvic capacity on the incidence of cesarean sections, necessary forceps, maternal morbidity, and fetal death is shown in Table III. These items were chosen because they seem to represent an index of the severity of pelvic deformity. Certainly this was true in the first series of 935 patients when interference of any sort was permitted only after it was obvious to all concerned that labor was arrested. In the present series it might be argued that the increasing incidence of cesarean section with decreasing pelvic capacity represents only the fear of the obstetrician. Such an argument is only partly true, since three-fifths of the patients with primary cesarean section experienced some hours of labor immediately prior to operation.

TABLE III. EFFECT OF PELVIC CAPACITY

PELVIS AREA CAPACITY (%)	NO. OF PATIENTS	CESAREAN SECTIONS (%)	NECESSARY FORCEPS (%)	MATERNAL MORBIDITY (%)	FETAL DEATH (%)
Both planes more than 90	2,163	1.9	5.3	11.8	2.5
90-86	637	3.0	4.2	8.0	0.3
Inlet only 85 or less	336	19.0	2.4	9.2	1.5
Midplane only 85 or less	398	24.6	4.8	12.1	1.3
Both planes 85 or less	238	50.4	4.2	14.7	3.8

When the preceding table is condensed into two groups, namely, normal and contracted pelves (Table IV), the difference in incidence of cesarean section is sharply dramatized.

TABLE IV. CESAREAN SECTION INCIDENCE

	NO. OF PATIENTS	CESAREAN SECTIONS	
		NO.	%
Normal pelvis Both planes 86 or more	2,800	60	2.1
Contracted pelvis Either or both planes 85 or less	972	282	29.1

The effect of isolated inlet contraction is seen in Table V. Forceps incidence is omitted, since isolated inlet contraction would have no influence on the incidence of any type of forceps operation we would care to do.

TABLE V. EFFECT OF ISOLATED INLET CONTRACTION

	NO. OF PATIENTS	CESAREAN SECTION (%)	MATERNAL MORBIDITY	FETAL DEATH (%)
85-81	204	10	9.0	1.5
80-76	89	24	7.9	1.1
75-71	34	47	1.4	3.0
70 or less	9	77	0.0	0.0

TABLE VI. EFFECT OF ISOLATED MIDPLANE CONTRACTION

	NO. OF PATIENTS	CESAREAN SECTION (%)	NECESSARY FORCEPS (%)	MATERNAL MORBIDITY (%)	FETAL DEATH (%)
85-81	259	14	5.4	0.9	0.4
80-76	87	33	4.6	1.6	0.0
75-71	48	65	2.1	2.1	2.1
70 or less	4	75	0.0	0.0	25.0*

*Child weighing between 1,500 and 1,999 grams died of atelectasis 48 hours after cesarean section following trial labor.

The effect of isolated midplane contraction is seen in Table VI. As the incidence of cesarean section rises the incidence of necessary forceps falls. By employment of radiographic pelvimetry, especially of the midplane, we have materially reduced, and almost eliminated, the midforceps operation. This has been achieved without much increase in the over-all incidence of abdominal delivery, because of improved ability to select patients.

A comparison of the effects of isolated inlet, isolated midplane, and biplanar contraction on the incidence of cesarean section is seen in Table VII. It follows expectancy except in 3 of the smallest pelves. Two of these women experienced spontaneous delivery. This represents a most significant reason why pelvic mensuration alone or with fetometry will not solve the problem of cephalopelvic disproportion.

TABLE VII. EFFECT OF CONTRACTION ON CESAREAN SECTION INCIDENCE
(REPEAT SECTIONS OMITTED)

	INLET	MIDPLANE	BIPLANAR
85-81	6	10	16
80-76	18	27	50
75-71	33	57	100
70 or less	71	67	33*†

*Para i. Spontaneous birth by vertex in less than 4 hours' total labor of living child who weighed between 2,000 and 2,499 grams. Cesarean section first pregnancy when the cervix was 4 cm. dilated because of failure of progress.

†Nullipara. Spontaneous birth by vertex in less that 12 hours of living child who weighed between 2,500 and 2,999 grams.

The effect of biplanar contraction on the incidence of abdominal delivery can be seen in Table VIII. Here again the imponderables of the five components of cephalopelvic disproportion assumed charge of the situation and two labors in one patient terminated spontaneously. True, the second labor with a large baby was slower than the first with a small child. Undoubtedly the youth of the patient contributed to the vigor of uterine force.

TABLE VIII. EFFECT OF BIPLANAR CONTRACTION ON CESAREAN SECTION INCIDENCE
(REPEAT SECTIONS OMITTED)

MIDPLANE CAPACITY	INLET CAPACITY			
	85-81	80-76	75-71	70 OR LESS
85-81	16	28	56	0*
80-76	52	50	67	67
75-71	45	43	100	100
70 or less	100	50	80	33

*Two spontaneous births, same girl, at ages 14 and 16. First labor less than 12 hours, child between 2,500 and 2,599, second labor less than 24 hours, child between 3,000 and 3,499 grams.

Finally, we have come to believe that under a given set of circumstances the young woman is more likely to experience spontaneous labor than an older one. Table IX dramatizes this belief. Unfortunately the number of women over 30 years of age is small. Therefore, the figures can be accepted only as indicating a possible trend.

TABLE IX. AGE AND CESAREAN SECTION INCIDENCE IN PRIMIGRAVIDAS
All patients submitted to trial of forces of labor. Pelvic capacity 85 or less.

UNDER 20 YEARS		OVER 30 YEARS	
NO. OF PATIENTS	NO. OF CESAREAN SECTIONS	NO. OF PATIENTS	NO. OF CESAREAN SECTIONS
436	15	18	22

Summary

After nearly 4,000 labors and eleven years of experience with interpretation of figures obtained by radiographic pelvimetry, and with the graphic area method of estimation of pelvic capacity, I believe we have been able to narrow the twilight zone of doubt regarding cephalopelvic disproportion. As pelvic capacity decreases, the probability of spontaneous birth decreases. Ultimately a point is reached where it is not a reasonable gamble to allow the patient to labor. Nevertheless, an occasional "long shot" will win through. These isolated exceptions sharpen the interest but do not alter the general rule.

Discussion

DR. DAVID N. DANFORTH.—I wish to comment upon certain of Dr. Mengert's tenets with which I am not in full agreement. My own interest in x-ray pelviography is considerable, and my objections should by no means be construed as indifference to this technique, or failure to appreciate its value. During my training at the Sloane Hospital for Women I was exposed for an extended period to the teaching and practice of W. E. Caldwell and Howard Moloy, whom I believe to be largely responsible for the establishment of x-ray pelviography as a useful clinical device. At the Evanston Hospital we employ a modification of their technique and find it invaluable, not only in clinical practice, but also in teaching.

One of the most rewarding aspects of an interest in x-ray pelviography is its inevitable relationship to practical clinical problems, and, consequently, its value as a teaching device. This is amply demonstrated in all of the essayist's papers dealing with this subject. The futility of external pelvimetry, the importance of the uterine forces, head molding, and position and presentation in evaluating cephalopelvic disproportion, and the philosophy of the test of labor are among the problems which are emphasized. These are important concepts, which Dr. Mengert's work has done much to clarify, and which reappear with great frequency in our own biweekly reviews of routine films.

I wish to comment specifically upon two features of the essayist's technique which I believe purport to give information which is actually not there, and which, accordingly, may give to the uninitiated an entirely spurious concept. I refer first to the implication that it is possible to predict, or even to estimate, cephalopelvic disproportion by *measuring* the size of the pelvis, and *clinically estimating* the size of the baby, as to whether it is small, medium, or large. One could not decide whether a piano would go through a doorway by measuring only the doorway. When the pelvis is huge and the baby small, the most casual examination will rule out disproportion. But when the discrepancy is small, no amount of intuition will allow an estimate of cephalopelvic relationships unless the diameters of both are known. It is not startling that a 15 per cent reduction in pelvic capacity, even when it is estimated by this method, should be accompanied by an increased incidence of difficult delivery. But if, in such a case, the biparietal diameter were also reduced by 15 per cent, no difficulty should be anticipated. Also, the patient whose pelvic capacity is increased by 5 per cent may have the greatest difficulty in delivering a baby whose biparietal is increased by 10 per cent. In the case of cephalopelvic disproportion, any prediction will, of course, depend upon the variables of head molding and uterine forces; but to have usefulness in a specific case, it is necessary to know not only the size and shape of the pelvis, but also the biparietal diameter of the fetal head. Accordingly, I believe that this method, and all others which do not measure the biparietal diameter, are not useful in estimating cephalopelvic disproportion. Furthermore, and on these same grounds, I object to the term "pelvic contraction" as an indication for cesarean section, in preference to the now less popular, but presumably synonymous, diagnosis of cephalopelvic disproportion. What one actually means, in a given case, is that a particular head is too large to go through a particular pelvis. To connote this set of circumstances there is no better term than cephalopelvic disproportion.

Second, I am satisfied that the mere mention of the anteroposterior and widest transverse diameters of the pelvis, and any possible arithmetic manipulation of these two figures, can give no notion whatever of capacity either at the inlet or in the midpelvis. A wedge-shaped android pelvis has an entirely different capacity, and a completely different clinical implication, from that of a relatively round gynecoid pelvis, even though the anteroposterior and widest transverse diameters of both may be identical. With an anteroposterior diameter of 11.5 and a widest transverse of 12.5, the gynecoid would probably permit the passage of a baby weighing at least a pound more than an extreme android pelvis of equivalent dimensions. Accordingly, although it is of interest that, when capacity is estimated by the method of Mengert, difficulty often arises when it is reduced by 15%, nevertheless I believe that this gives little insight into the individual case. Furthermore, in the reporting of x-ray pelvimetry, and for the reason just mentioned, I believe it is of the greatest importance to report not only the anteroposterior diameter and the widest transverse, but also, at the inlet, to report both the posterior and the anterior sagittal diameters. From these latter measurements, it is instantly evident whether one deals with an android or a gynecoid inlet, which may be of the greatest importance in prognosis.

Finally, I believe it should be pointed out that one of the greatest fields of usefulness for x-ray pelviography is not the determination of cephalopelvic disproportion, but rather the prediction of the optimum mechanism of labor at the various pelvic planes, and also as a guide to the proper performance of midforceps operations as they may be necessary. These data are available in Dr. Mengert's work, but do not receive the needed emphasis. Caldwell and Moloy have demonstrated, and it has been amply confirmed, that where all of the available space is used the occiput tends to rotate to the widest part of the pelvis at any given level. Also, the biparietal diameter, being the narrowest diameter of the head, tends to traverse the narrowest diameters of the pelvis. Applying these tenets, it is possible in many of the cases which cause concern to predict the optimal mechanism, and thus to effect midforceps delivery in the proper diameters.

DR. WILLIAM J. DIECKMANN.—I am in doubt as to whether the author favors pelvic mensuration or deems it not essential. He first reported about 1,000 cases and then had 3,000 more. Do these figures represent all the cases delivered on his service in 11 years or do they represent a selected group?

Dr. Hodges, in our Department of Radiology, developed orthographic pelvimetry and he and Dr. Davis used this method in 912 primiparous white women. He has reported the radiologic findings and concludes that there are dystocias of many sorts "and it is rash indeed for the radiologist to assure the obstetrician that this woman will deliver easily, that one with difficulty or not at all."

No obstetric study has, as yet, been made, but the fact that we make less than 20 x-ray mensurations per year indicates that we see no need for extensive use of this method. The day will come when the size of the baby and its head can be measured accurately in utero and there will be some method for determining early in labor the uterine force. With these three factors plus x-ray pelvic mensuration, one will be able to foretell the outcome of labor more accurately than even the expert clinician can do today.

DR. MENGERT (Closing).—I would not have Dr. Danforth think that if we get a couple of measurements from here and a couple from there and without looking at the x-ray plate we can come up with the answer. Far from it. We started out by trying to measure the fetal head but finally gave it up. I think clinically it is possible to tell whether the head is large, medium, or small. This has helped to give us some idea of what is going to happen in labor. One of the papers written by our group some time ago was aimed at predicting the outcome of labor. With measurements of the inlet and midplane, a graphic outline of the contour of each, and then fitting a plastic head to the contours, it was surprising what we could predict about labor.

We used to measure the anteroposterior and the posterior sagittal both of the inlet and midplane. Finally we gave up the posterior sagittal because we did not believe it gave

enough information. You are all familiar with the rule of 13.5 that was devised for the outlet by Williams. You might be interested to know that 2 patients, both with a sum of less than 12 cm. for the transverse and posterior sagittal of the midplanes, had spontaneous births of average-sized children.

I am all *for* pelvic mensuration and I am not against it. We try to do it in all primigravidas and we have tried to do it in multigravidas who have a history of difficult labor or any physical finding of distortion of the sacrum or pelvis.

I know of two places where radiographic pelvimetry is of inestimable value. One is with the aftercoming head and the other with uterine inertia, when labor is unusually prolonged. If one has knowledge that the inlet and midplane have a capacity of 100 per cent or better, one can approach the management of the prolonged labor with a great deal of confidence.

We have given up teaching manual mensuration. We try to teach the clinical "criteria of suspicion." I feel that anyone of these clinical criteria, when present in any given patient, should warrant the use of x-ray pelvimetry.

LABOR COMPLICATIONS AND CEREBRAL PALSY

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IT MIGHT be said of William J. Little, as of few of his fellow physicians of a century ago, that if he returned to the medical scene today he would find himself on quite familiar ground. At least this would be true of one of his chief interests, the etiology of the condition now known as cerebral palsy. In Little's day as in our own the attempt to relate cerebral palsy to events of the perinatal period gave rise to disputes that were chiefly conflicts of inference, proof in this field being difficult to come by. We are unfortunately still in the position of seeking reliable answers to many of the questions raised by Little and successive investigators.

The following presentation is based on a study of 204 cerebral palsied children, certain clinical aspects of which have already been reported.[1] The obstetrical data of the study have been reduced to statistical form and are presented here in a series of charts, chiefly with the aim of providing the obstetrician with factual material for evaluation in the light of his own experience. While directing attention to some conditions which undeniably form a background for cerebral palsy in general, and to others seemingly related to certain types of cerebral palsy, the charts are not thought to portray cause-and-effect relationships. The reliable answers are still in the future. It is believed, however, that the definitive clinical studies to come can be carried out to greatest advantage along lines developed in this investigation.

Infantile cerebral palsy has traditionally been viewed as due to heredofamilial defect,[2] maternal disease during pregnancy,[3] or complicated labor, the latter being Little's[4] concept. Obstetricians, on the whole, have been open-minded but skeptical regarding the role of abnormal labor.[5, 6, 7] Eastman and DeLeon,[8] however, having carefully studied the perinatal circumstances of infants who later developed cerebral palsy, recently came to the conclusion that the majority of their cases were of "obstetrical etiology." A similarly striking incidence of labor complications in our own cases led to the present compilation and analysis of our obstetrical data.

Materials and Methods

The basic sources of information in the present study were the hospital records (birth and neonatal) of 204 cerebral palsied children examined at the Newington Home and Hospital for Crippled Children, Newington, Connecticut, during the past 6 years. Only children with available hospital records were included in the study. The group of 204 cases was selected from a referred

clinic material of 667 children, of whom 507 were found on examination to have cerebral palsy. The method of selection is outlined in Fig. 1. The objective was to obtain reasonably homogeneous groups of patients in terms of central nervous system involvement, the assumption being that like syndromes would probably have like etiologies. An effort was made to eliminate children with other than motor defects, a complication of defects perhaps pointing to a complication of causes. After cases with incomplete records were dropped, therefore, further eliminations were made of noninfantile types of cerebral palsy (cases of known etiology), mentally defective and epileptic children, and children with the less common variants of cerebral palsy. The study was thus narrowed to a group of purely motor-handicapped children with but few complicating defects. The process of selection has been emphasized, since the findings of the study are not taken to apply equally to unselected material.

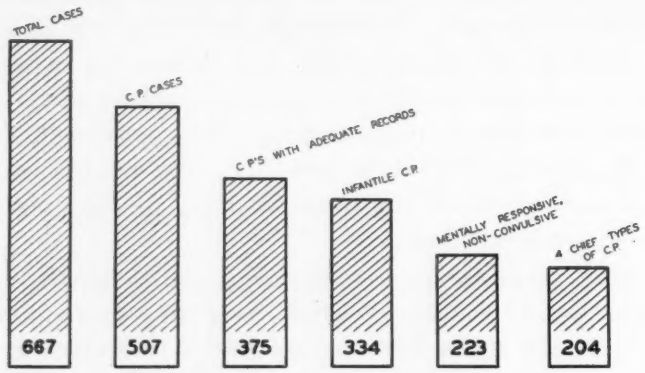

Fig. 1.—Selection of case material.

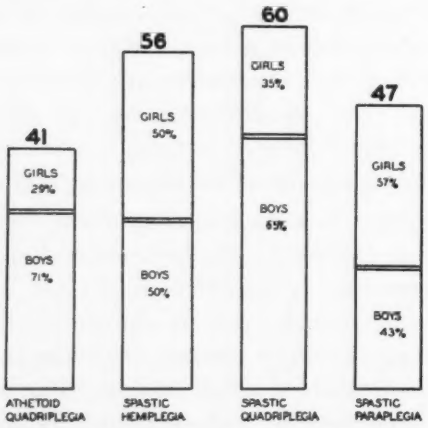

Fig. 2.—Number of cases and sex distribution in the four diagnostic categories of the study.

Our patients were divisible, on the basis of neurological involvement, into 4 groups: athetoid quadriplegia (41 cases), spastic quadriplegia (60), spastic hemiplegia (56), spastic paraplegia (47). The sex distribution in each of these groups is shown in Fig. 2.

Cerebral palsy may be classified according to several methods, the one used here being simple and self-explaining. Athetoid children have uncontrollable movements, spastic children are "tight." Perhaps the types of cerebral palsy are nodal points on a continuum rather than different entities; at any rate, one encounters patients with mixed characteristics bridging the types.

While virtually all studies of labor in cerebral palsy note an increased incidence of perinatal complications, a basis for comparison is not usually available. Two exceptions are the article of Eastman and DeLeon already cited and a study of Lilienfeld and Parkhurst.[9] In the present study comparative statistics were obtainable from the Registration Reports issued annually by the Connecticut State Department of Health. These reports summarize information on the large majority of deliveries performed in the state, complications of labor being recorded by the attending physician on a supplemental report attached to the birth certificate. While not a control group, these deliveries at large constitute the population from which our patients are derived, and hence provide a reasonable basis for comparison, subject to reservations that will be mentioned. The Registration Report for the year 1948[10] was selected as central for the age distribution of the study, which was largely the 2- to 19-year-old range, younger children predominating. The expectancies given in Figs. 3, 5, and 6 derive from this Report. The curve illustrating normal birth weight distribution (Fig. 4) was plotted from published figures for live white births in New York City[12] since the Registration Report does not break down birth weights under 1,500 grams.

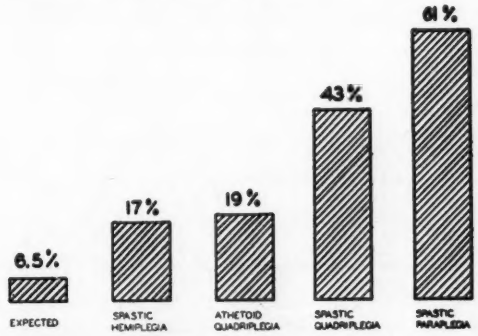

Fig. 3.—Incidence of prematurity (infants of birth weight less than 5½ pounds) in four diagnostic categories of cerebral palsy, compared with expected (normal) incidence.

Analysis of Findings

Our data of sex incidence are of interest in showing that the male preponderance in cerebral palsy, which has long been recognized,[11] appears restricted to the athetoid and spastic quadriplegia forms of the disease (Fig. 2). In these two groups the excess of males may be a function of their greater birth weight: it will be pointed out later that certain types of maternal dystocia apparently related to cerebral palsy occur more commonly with heavier infants. Another sex linkage disclosed in Fig. 2 is an evident excess of females in spastic paraplegia. In view of the high incidence of prematurity in this type of cerebral palsy the sex distribution may be related to the lower mortality rate of female as compared with male infants under 3,000 grams.[12] One cannot be certain, however, of the validity of so small a preponderance in a series of this size.

While Little's original observation of the association of prematurity and cerebral palsy has been repeatedly confirmed, the extent to which this association depends on the spastic quadriplegia and paraplegia groups is not widely appreciated. The incidence of prematurity in these two groups is double or triple that in athetoid quadriplegia or spastic hemiplegia (Fig. 3). It should also be noted that in the latter two groups the birth weight distributions follow curves more or less like the normal, while in spastic quadriplegia and paraplegia the curves are bimodal, tending to follow each other, the greater number of small infants being in the paraplegia group (Fig. 4).

The variation from the expected birth weight distribution in each of the 4 groups has been tested against distribution of Connecticut live births (1951) and has been found to be well beyond chance occurrence.* In Figs. 5 and 6 statistical validation of differences from expectancy has not been attempted since without genuine control techniques no absolute reliability can be attached to the differences shown.

A child of markedly low birth weight—below 2,000 grams—is far more likely to have spastic paraplegia or spastic quadriplegia than other forms of cerebral palsy. Of the 4 diagnostic groups spastic hemiplegia most nearly follows a normal weight distribution. When it is recalled that the sex division in this group also approximates the normal (Fig. 2), it seems possible that the unknown factors of preselection obtaining in other cerebral palsy groups do not apply to spastic hemiplegia.

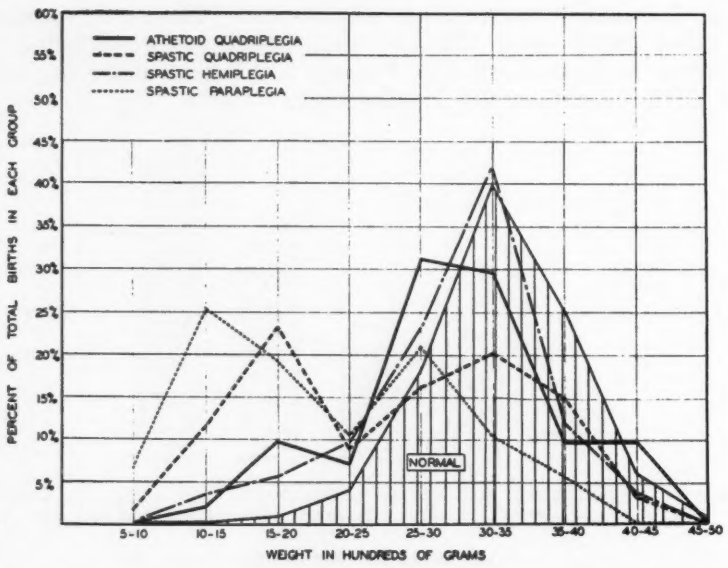

Fig. 4.—Distribution of birth weights in four categories of cerebral palsy and in a normal population.

In view of the high incidence of prematurity in cerebral palsy it might be anticipated that labor complications known to be associated with prematurity, such as breech presentation and vaginal bleeding, would occur more frequently than in term pregnancies, especially in the spastic quadriplegia and spastic paraplegia groups. This is borne out by the data of the study. These complications seem to occur, however, at a higher rate than might have been foreseen (Fig. 5). Breech presentation reaches an incidence of some 15 per cent in spastic paraplegia; in spastic quadriplegia its incidence is even higher. Since there is less prematurity in spastic quadriplegia than in paraplegia, factors other than prematurity alone evidently account in part for the high incidence of breech presentation in the former. We cannot tell from present data whether such factors relate to the special hazards of breech delivery.

Antepartum hemorrhage, in large part attributable to placenta previa and premature separation of the placenta, also occurs more frequently in spastic quadriplegia and paraplegia (Fig. 5). (For the purpose of this study

*For this information and for other statistical assistance I am indebted to Mr. Robert J. Keehn, Director of Bureau of Vital Statistics, Connecticut State Department of Health.

antepartum hemorrhage has been taken to mean vaginal bleeding within a few hours of beginning labor. The term is not defined in the Registration Report.) In spastic hemiplegia, where the incidence is lower, antepartum hemorrhage still occurs about once in every 20 deliveries, sometimes constituting an indication for cesarean section. Prematurity taken into account, spastic hemiplegia seems to be the only one of the four diagnostic groups with a cesarean section rate much above expectancy (Fig. 5). One cannot begin to assess the significance of this operative rate without detailed consideration of the preoperative course of labor in each case.

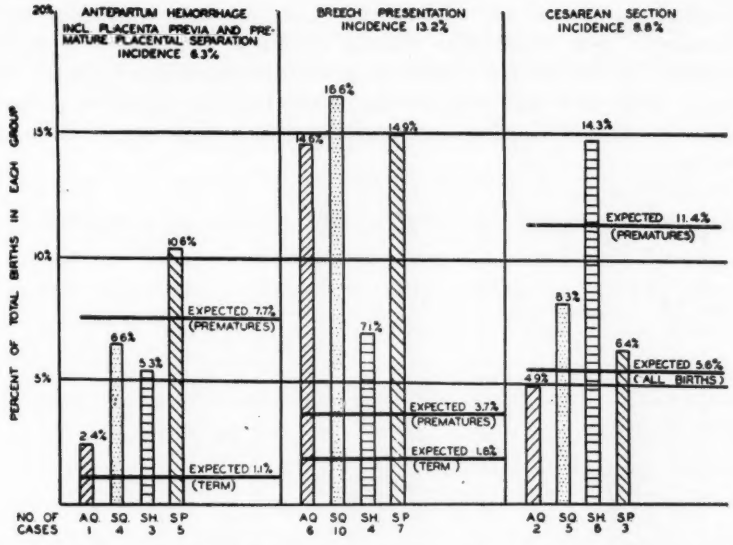

Fig. 5.—Incidence of antepartum hemorrhage, breech presentation, and cesarean section in four types of cerebral palsy, versus expectancy in a general population.

A.Q., Athetoid quadriplegia.

S.Q., Spastic quadriplegia.

S.H., Spastic hemiplegia.

S.P., Spastic paraplegia.

In Figs. 5 and 6 the "number of cases" (bottom line) refers to the number of times the listed condition occurred in each of the four diagnostic categories.

Not shown in the figures but of incidental interest: Twinning was of high occurrence in the spastic quadriplegia and paraplegia groups (5 and 6 pairs, respectively), and precipitate births seemed relatively frequent. Of the 13 pairs of twins in the case material the patient was first born in 7, second born in 6, suggesting that, so far as this small number goes to show, the liability to cerebral palsy in twins is not related to birth order. It is very unusual for infantile cerebral palsy to occur in both members of a set of twins, and there was no such instance in this series.

Labor complications based on difficulties of passenger in relation to the passages can readily be shown to increase with increasing weight when cerebral palsied children are listed in order of birth weight.[1] An indication of this type of dystocia is given in the apparently high incidence of labor arrest in all cerebral palsy groups except spastic paraplegia, the rate for athetoid quadriplegia being about 1 case in 5 (Fig. 6). The headings of Fig. 6 from left to right (persistent transverse or posterior position; arrest of labor; high and midforceps application) suggest a sequence not infrequently encountered in the birth histories of these athetoid children. While the arrest was usually

ascribed to persistent posterior or transverse position of the head, at times it seemed associated with uterine inertia or the complications of breech delivery.* In the resolution of labor arrest, high and midforceps applications appear to have been resorted to rather often (Fig. 6). It may also be mentioned in passing that neck encirclement by the umbilical cord occurred 5 times in the athetoid group of 41 cases, 7 times in the spastic hemiplegia group of 56 cases.

What role does maternal disease play in cerebral palsy? Some few cases in our original clinic material that were clearly of origin during pregnancy—chiefly children with kernicterus following maternal Rh isoimmunization—were eliminated in selecting the present series. Subsequent review of the records included in the study failed to turn up any striking incidence of maternal disease.[1] An exception should perhaps be made of spastic hemiplegia, where of the total of 56 cases 6 mothers had some type of illness during pregnancy. But one scarcely needs to read many of these pregnancy records to realize how speculative conclusions along this line can be in the absence of controls.

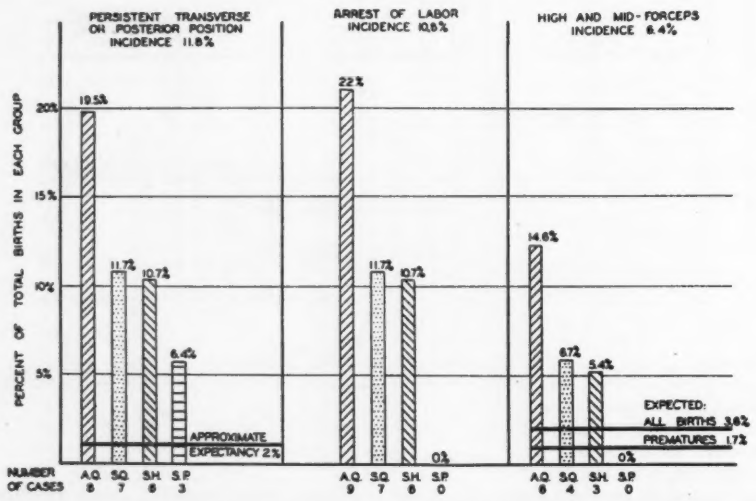

Fig. 6.—Incidence of persistent transverse and occiput posterior position, arrest of labor, and high and midforceps applications in four types of cerebral palsy (partly) compared with incidence in a general population. Abbreviations as in Fig. 5. The partial duplication of percentages in the left and middle sections of the figure is coincidental, identical cases not being represented.

Summary

This discussion has included reference to a number of the chief complications of labor. A tentative correlation, chiefly as a matter of clinical interest, can be set up between certain of these complications and one or more types of cerebral palsy. An inevitable relationship between cerebral palsy and a given complication of labor is of course not implied. Clinically speaking, we ought to think in terms of a progression of causes which finally exceeds the limit of fetal tolerance. Although many obstetricians may already have reached a similar conclusion it is worth mentioning because the potential significance of complicated labor sometimes seems diminished when a group of infants can be shown to have survived it largely unscathed.[6]

*The salient features of labor in many of the cases included in this study have been presented elsewhere[1] in the form of individual case summaries.

From the obstetrical standpoint the results of this study may then be summarized in the following table of correlates, submitted for their suggestive value until better ones are developed. The correlates are not meant to be exclusive from group to group; to some extent all forms of cerebral palsy share the same background. A comparison of these correlates with the schema of Perlstein,[13] who was the first to draw up a table of correlates for cerebral palsy, may be of interest.

Athetoid quadriplegia: Persistent malposition, breech presentation, cord encirclement, arrest of labor, mid- or high forceps application.

Spastic quadriplegia: Prematurity, breech presentation, detachment of the placenta.

Spastic hemiplegia: Cord encirclement, maternal illness.

Spastic paraplegia: Prematurity, breech presentation, detachment of the placenta.

The Pathogenic Mechanism in Cerebral Palsy

If the onset of cerebral palsy occurs during the perinatal period in most instances, two primary mechanisms may be responsible: intracranial hemorrhage or anoxia. There are numerous reasons, none conclusive, for ascribing a primary role to anoxia. Intracranial hemorrhage in the form of subdural hematoma of the newborn is a well-recognized entity the clinical course of which differs in some respects from that of most cases of cerebral palsy in the neonatal period.[14] It must nevertheless be granted that some cases of cerebral palsy are very likely of this origin. Intraventricular and subarachnoid hemorrhages are said to absorb without organization,[15, 16] and in any event seem to be secondary to anoxia.[17] Some of the obstetrical complications which may antecede cerebral palsy, such as bleeding from the placenta and looping of the cord, appear to be purely anoxic mechanisms; in at least one inadvertent experiment in man anoxia was shown to produce a cerebral palsylike syndrome.[1] According to Courville[18] the pathological lesions of cerebral palsy are compatible with anoxia as the origin. Courville notes that the various lesions "are found in almost every possible combination." In dealing with cerebral palsied patients clinically one gets the impression that the pathogenic mechanism of this disease must be one capable of infinite gradations, since qualitative and quantitative differences of neurological involvement are always present from one patient to the next. Finally, assuming that the ability of the obstetrician to avert traumatic labor has undergone constant improvement in this country during the past few decades, we have yet to see any indication of a decrease in the incidence of cerebral palsy. Even if a primary role is correctly assigned to anoxia, intracranial bleeding must still be of great significance; the two pathogenic mechanisms are inextricably linked.[17] In most cases in this series anoxia appears to have been the primary mechanism.[1]

Since Little first proposed abnormal parturition and asphyxia neonatorum as causes of cerebral palsy their etiological roles have been repeatedly affirmed and as often denied. We have yet to arrive at anything like a final answer. Probably all observers concede that some cases of cerebral palsy are of obstetrical origin, but how many, and, most importantly, why? The birth histories

of cerebral palsied children may often be matched, apparently evenly, with those of normal infants. What combination of circumstances so fatefully stamps the former? It was probably easier in Little's day than now to attempt answers to these questions. The almost universal use of anesthesia and analgesia in obstetrics, modern techniques for salvaging premature and marginal newborn infants, the availability of operative methods of delivery—these have introduced complexities unknown to Little. To evaluate all of the possibly contributory factors in cerebral palsy a broad and well-planned clinical study is needed, based on forward rather than retrospective data. The complications of labor and events of the perinatal period offer the most promising area of approach to a better understanding of cerebral palsy and of the methods which must be developed to prevent it.

Conclusions

1. The incidence of prematurity is markedly increased among infants who develop the spastic paraplegia and spastic quadriplegia types of cerebral palsy. Increased prematurity occurs to some extent in all types of cerebral palsy.

2. There appears to be an increased incidence of complications of labor in cerebral palsy. The complications which seemed of contributory importance in this study were chiefly persistent malposition, breech presentation, arrest of labor, mid- and high forceps applications and premature separation of the placenta.

3. The usual pathogenic mechanism in cerebral palsy appears to be cerebral anoxia.

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THE USE OF NYSTATIN IN THE TREATMENT OF VAGINAL CANDIDIASIS IN PREGNANCY

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PREVIOUS in vitro studies in our laboratory[8] indicated that strains of *Candida albicans* are rather uniformly susceptible to the action of nystatin.* This suggested that nystatin might be a useful drug for treating localized infections with this organism.

C. albicans is a common cause of vaginitis in pregnancy. Henricksen and his associates[3] cultured *C. albicans* from the vaginas of 61.2 per cent of 72 gravidae with symptoms of vaginitis. However, the finding of *C. albicans* in the vagina does not in itself indicate disease. Normal women can harbor the fungus, especially in pregnancy.[2] For example, Henricksen's group[3] found *C. albicans* in 30.2 per cent of 162 gravidae that had no symptoms of vaginitis. Whether or not Candida species other than *C. albicans* may cause vaginitis will not be debated here. It is known, however, that *C. albicans* is by far the most common species to be found on culture, although others, such as *C. krusei* have occasionally been reported as associated with clinical vaginitis.[3] Other investigators,[1, 4] in treating vaginal candidiasis of pregnancy with propionate jelly, have found little correlation between relief of symptoms and the results of a posttreatment culture. With most forms of treatment hitherto employed, relief of symptoms has been much easier to accomplish than eradication of the organism from the birth canal. Delivery usually results in cure of otherwise untreated patients.[4, 7]

With these factors in mind, a group of pregnant patients with vaginal candidiasis was treated with nystatin vaginal tablets.†

Materials and Methods

Using patients in the prenatal clinic of the Philadelphia General Hospital, vaginal cultures for *C. albicans* were taken from 155 patients who complained of pruritus vulvae or vaginal discharge. Sixty-five of these patients had positive initial cultures but, of this group, 41 patients had to be eliminated from consideration for various reasons: chiefly, failure to return for follow-up examination, failure to use treatment as prescribed, and delivery within 3 weeks of starting treatment. The remaining 24 patients are included in this study.

*An antibiotic substance isolated from cultures of *Streptomyces noursei*. It is an optically active, amphoteric substance which has the empiric formula $C_{46}H_{77}NO_{19}$.

†Supplied by Dr. H. A. Strade, Associate Medical Director of E. R. Squibb and Sons Division, Olin Mathieson Chemical Corp., New Brunswick, N. J. The trade name of E. R. Squibb and Sons for nystatin is Mycostatin.

These 24 women were all Negroes in the second, or early third, trimester of pregnancy. Their average age was 22.3 years, with a range of 16 to 36 years. The average parity was 1.9. No diabetic patients were included and all were in good general health except for the following: one patient had preeclampsia superimposed on essential hypertension; one had hypertensive cardiovascular disease and pyelonephritis; one had inactive, compensated rheumatic heart disease; and one was schizophrenic. Anemia was common. The average hemoglobin was 11.2, with a range of 7.8 to 14.1 mg. per 100 ml.* Associated local conditions included one case of condylomata acuminata and one of chronic cervicitis. Thirteen patients complained of both vaginal discharge and pruritus, the rest of discharge alone. Initial examination in all cases revealed more than usual vaginal discharge but not always the "classical" picture of cheesy white plaques adherent to an inflamed mucosa. This picture was seen clearly in only 8 of the 24 cases.

The drug was used in the form of 100,000 units of nystatin dispersed in a lactose tablet. A treatment course consisted of one tablet inserted twice daily for 2 weeks on arising and retiring. Douches were not advised. Most of the patients stated that they used the tablets "most of the time." Repeat cultures were taken between 2 and 4 weeks after the start of treatment and in all cases were taken before delivery. Cultures were made by inoculating a moist vaginal swab onto plates of Sabouraud's glucose agar and bromthymol blue lactose agar. Both were incubated at room temperature and observed daily for a maximum of 6 days. Typical yeastlike colonies appearing within this period were subcultured onto cornmeal agar plates at room temperature and observed up to 3 days for the mycelia and chlamydospores of *C. albicans*. If well-developed mycelia, but no chlamydospores, appeared, the colony was transferred to another cornmeal agar plate and again observed 3 days for the development of chlamydospores.

Results

Initial vaginal cultures in 155 pregnant clinic patients with symptoms of vaginitis were positive for *C. albicans* in 65 cases (41.9 per cent). Of 24 patients with positive initial cultures, 22 (92 per cent) were symptomatically improved during and after treatment. Posttreatment cultures were taken from 20 patients; they remained positive in 10 (50 per cent) and became negative in 10 (50 per cent). There was no apparent correlation between symptomatic improvement and disappearance of *C. albicans* from the vagina (Table I).

TABLE I. RESULTS OF TREATMENT IN 20 PATIENTS FROM WHOM POSTTREATMENT VAGINAL CULTURES FOR *C. albicans* WERE OBTAINED

POSTTREATMENT CULTURE			SYMPTOMATIC RESPONSE			
			IMPROVED		PERSISTED	
	NO.	%	NO.	%	NO.	%
Positive	10	50	10		0	
Negative	10	50	8		2	
Total	20	100	18	90	2	10

No symptoms of primary drug irritation were reported, and no toxic effects were observed. One patient, a 36-year-old multipara with hypertension and pyelonephritis, was delivered of a stillborn child at 33 weeks' gestation, 2 weeks after stopping nystatin treatment. Another, a healthy 27-year-old multipara (not included in the above series), had vaginal bleeding, followed by expulsion of a nonviable 20 week fetus. This occurred 2 days after stopping nystatin treatment. Other patients were delivered normally.

*Determinations were done on 0.1 ml. venous blood with the use of an Evelyn photoelectric colorimeter.

Comment

Although we recognize the pitfalls of comparing clinical studies done under different conditions, we shall mention the results of a few previous studies on vaginal candidiasis in pregnancy.

Using a propionate vaginal jelly for 2 to 3 weeks, Kantor[4] reported symptomatic improvement in 75 per cent and culture conversion in 45 per cent of 38 patients. With similar treatment, Alter and his associates[1] obtained relief of symptoms in 100 per cent and culture conversion in 33.3 per cent of 24 patients. Reich and his co-workers,[5] using a 3 week course of treatment with the sodium and zinc salts of caprylic acid, obtained negative posttreatment cultures in all of 17 gravidas, together with rapid symptomatic relief. Waters and Wager,[7] using 0.2 per cent gentian violet in an acid polyethylene-glycol base, obtained disappearance or improvement of symptoms in 93 per cent of 191 pregnant patients, and 3 negative posttreatment smears in 90 per cent. Previously published reports[6, 9] of treatment with nystatin failed to state whether or not the patients were pregnant.

Results in our series, both as to symptomatic relief and culture conversion, appear quite similar to those obtained with propionate jelly. Culture conversion in our series was considerably lower than in patients treated with caprylates.[5]

The fetal death at 33 weeks' gestation was attributed to the mother's systemic diseases. The significance of the expulsion of a 20 week fetus 2 days after cessation of therapy is not apparent, but there is no evidence to incriminate the vaginal therapy as an etiological factor.

Summary and Conclusions

1. Vaginal cultures from 155 untreated pregnant women with vaginal discharge or pruritus were positive for *C. albicans* in 65 cases (41.9 per cent).

2. Twenty-two of 24 gravidas treated for vaginal candidiasis with nystatin vaginal tablets showed symptomatic improvement during and after treatment.

3. No correlation was apparent between symptomatic improvement and conversion of cultures to negative.

4. Nystatin vaginal tablets appear to be a satisfactory preparation for the treatment of vaginal candidiasis in pregnancy.

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COMBINED INTRA- AND EXTRAUTERINE PREGNANCY*

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COMBINED intra- and extrauterine pregnancy should be considered in the differential diagnosis of twins, ectopic pregnancy, and abortion whenever conflicting signs or symptoms are present. The diagnosis of this uncommon entity is frequently missed, causing an increase in maternal morbidity, and jeopardizing the life of the mother. The finding of placental tissue in the uterine cavity at the time of abortion often lulls the obstetrician into a false or incomplete diagnosis, and many ectopic pregnancies may go unrecognized until rupture. Normal intrauterine pregnancies may be neglected or needlessly sacrificed, thereby reducing fetal salvage.

Many excellent reviews on the subject have appeared in the literature, with the collection of a fairly large series of cases. The latest comprehensive review by DeVoe and Pratt[1] in 1948 included 395 authentic cases of combined pregnancy. To this list, we have added 68 cases reviewed from the world literature up to Dec. 31, 1954.[5-50] Three new cases herein presented by us bring to 71 the total number of cases in this critical analysis, and bring to a total of 466 the number of documented cases of combined pregnancy.

In the terminology of combined pregnancy it is implied that the pregnancies must coexist in a live state at some time, resulting from one fertilization or two separate fertilizations within a relatively short period of time.[1] It seems fairly certain that the large majority of these cases are twin pregnancies which originate from a single coitus and have separate sites of implantation, one of which is by definition the uterine cavity. Because it has never been shown that monozygotic twins can be partitioned and then choose two different sites of implantation, it must therefore be assumed that all combined pregnancies are the result of the fertilization of two ova. It may be postulated that these ova usually arise from two different follicles in one or both ovaries, or may even, on occasion, arise from the same follicle, as evidenced by the occasional finding of a single corpus luteum at the time of operation.[33] Faxon (by DeVoe[1]) expressed the opinion that in 10 per cent of cases of coexisting intra- and extrauterine pregnancy, the former is superimposed on the latter after an interval of time, varying from a few days to a period of years (superfecundation or, rarely, superfetation). Many of these, however, would more properly be termed compound pregnancies. In the cases in which the intrauterine pregnancy precedes the ectopic gestation, it seems obvious that the

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obliteration of the uterine cavity by the approximation of the decidua capsularis and the decidua vera would make it impossible for the time interval between the two implantations to exceed three months.[5] However, this cannot explain two cases described by Ludwig,[1] in which early ectopic pregnancies were discovered coexistent with viable intrauterine pregnancies.

In the pathogenesis of combined pregnancy it can be logically assumed that, regardless of the time of ovulation or fertilization, one ovum proceeds normally to the uterine cavity, while the other one becomes arrested in its course. The failure of the ovum to pass into the uterine cavity may be due to any of the following causes: (a) failure of the fimbrial end of the tube to catch or aspirate the ovum immediately; (b) infantile anatomical or physiological features of the tube, diverticula and other malformations; (c) nervous or anatomical disturbances of the process of propulsion through the tube by the mechanisms of endotubal flagellation and/or peristalsis; (d) pathological changes in the tube, caused by previous inflammation, kinking, adhesions from previous surgery, or other mechanical obstruction; (e) increased receptivity of the tube or hormonal narrowing of its lumen due to the previously established intrauterine pregnancy; (f) delayed implantation in the case of transperitoneal migration. The ovum may then be too large to pass the lumen of the contralateral tube.[16] One such case[42] is among the 68 cases reviewed from the recent literature.

Since it has been postulated that all combined pregnancies arise from two ova, it seems logical to assume that the ratio of single pregnancies to fraternal twins should hold true for both normal uterine gestations and for multiple pregnancies in which one is implanted ectopically. Thus one would expect the occurrence of a combined pregnancy in approximately 0.8 per cent[1] of all ectopic pregnancies, which figure would include also the much rarer instances of bilateral tubal pregnancies and fraternal twins in one tube. Kinnunen and Järvinen[2] investigated 1,263 consecutive cases of operation for ectopic pregnancy and found only 6 cases of combined pregnancy, or an incidence of 0.48 per cent, which is approximately one-half the expected figure.

When the incidence of fraternal twins is correlated with the incidence of ectopic pregnancy, combined pregnancy can be expected to occur once in every 30,000 gestations, an expected incidence of 0.003 per cent.[1] If this is true, then it seems certain that many cases go undiagnosed, or that only a small number of these cases has been reported. Frequently, the diagnosis may be missed when patients are treated in two different institutions or by two different physicians, and where all the facts are not known or not believed. Also, since nearly all reports originate in larger medical centers wherein the incidence of pathological findings is usually higher and diagnostic acumen greater, the figures reported may not reflect a true picture. However, the occasional occurrence of this entity warrants consideration in all cases of abortion or ectopic pregnancy.

Case Reports

CASE 1.—Mrs. M. C., a 25-year-old married white woman, gravida iii, para 0, was admitted on Sept. 2, 1950, with complaints of severe abdominal pain, nausea, vomiting, and vaginal spotting. This was associated with epigastric distress, weakness, and anorexia. Her last menstrual period had occurred on May 21, 1950, and she subsequently had a spontaneous abortion. A curettage for retained placental tissue was performed on July 25, 1950. Her present complaints began a week later, after she had been discharged from the hospital apparently improved, and had become gradually worse with occasional remissions.

Examination showed the patient to be pale, somewhat drawn, and complaining of constant lower abdominal pain. Her blood pressure was 128/88, temperature 98.8° F., and pulse 100 per minute. The upper abdomen was tender but soft. There were marked tenderness and rebound tenderness throughout the lower abdomen, and a firm fixed mass

was palpable extending upward from the pelvis, the size of a 12 to 14 weeks' gestation. On vaginal examination, the mass consisted of three portions, a small anterior one just above the symphysis, and a larger, firmer one above and behind, and adherent to the former. In the region of the right adnexa, a soft sausage-shaped mass was found which extended into the cul-de-sac. There was a small amount of thick dark-red mucoid secretion at the cervical os. The red blood count was 2.72 million with hemoglobin 8.5 Gm. per 100 c.c. The white cell count was 5,200 with 56 per cent segmented cells. The sedimentation rate was 37 mm., corrected. The Aschheim-Zondek test was negative, and x-ray revealed a dense homogeneous shadow in the pelvis.

The patient's general condition improved on supportive therapy with penicillin, whole blood, fluids, etc., but her abdominal symptoms and findings remained constant. A preliminary diagnosis of postabortal sepsis was discarded in favor of the alternate diagnosis of ectopic pregnancy with encapsulated hematocele, and on the seventh hospital day a laparotomy was performed through a lower midline incision.

The right tube was markedly distended with old blood, adherent to a large hematocele which was in turn adherent to the uterus. All these structures were bound together and to adjacent bowel by thin fibrinoid adhesions. The hematocele was removed and a right salpingo-oophorectomy performed. Except for a few thin adhesions, the left adnexa were normal. The pathological report revealed an ectopic pregnancy in the right tube and a hematocele containing a 3 cm. fetus. The postoperative course was uneventful, and the patient left the hospital on the eighth postoperative day in good condition.

CASE 2.—Mrs. M. T., a 29-year-old married white woman, gravida iii, para ii, was admitted on Feb. 3, 1950, with a history of sudden onset of sharp knifelike pains in the lower abdomen three hours prior to admission. The pain was constant and became worse on motion, causing the patient to double up and to feel faint. She was nauseated but did not vomit. Her last menstrual period had occurred on Dec. 15, 1949. On Jan. 20, 1950, she had spotted for a few days, and two or three days prior to admission she had experienced vague cramps in the lower abdomen.

Examination showed marked pallor and extreme restlessness. The blood pressure was 104/60, the pulse 68 per minute, and the temperature normal. There was a slight protrusion of the abdomen below the umbilicus, and tenderness and rebound tenderness were present throughout the lower abdomen. Pelvic examination disclosed a mass the size of a grapefruit in the right adnexa, and a somewhat softened uterus, enlarged to the size of a 6 to 8 weeks' pregnancy. The cervical os was closed. The admission red blood count was 3.6 million, hemoglobin 58.3 per cent, and the white cell count 21,000 with 78 per cent segmented cells and 11 per cent stab forms. The primary diagnosis was ruptured ectopic pregnancy of the right tube, although the possibility of a twisted ovarian cyst with intrauterine pregnancy was considered. Vaginal examination under general anesthesia showed bulging of the cul-de-sac, and colpocentesis produced several milliliters of a nonclotting free-flowing bloody fluid.

Laparotomy revealed a right ectopic pregnancy with perforation of the ampulla, and spongy tissue protruding through the perforation. There were much free blood and clots in the abdominal cavity. The uterus was slightly enlarged, soft and somewhat bluish. A right salpingectomy was performed, and the pathological report showed a right tubal pregnancy and placental tissue. The patient was discharged in good condition on the eighth postoperative day.

Examination four weeks later showed obvious enlargement of the lower abdomen, and pelvic examination revealed the uterus to be soft, and enlarged to the size of a 10 to 12 weeks' gestation. The uterine pregnancy continued uneventfully, and the patient was delivered, without complications, of a full-term, 7½ pound normal male infant on Sept. 19, 1950.

CASE 3.—Mrs. B. S., a 26-year-old married Negro woman, gravida iii, para ii, was admitted to Cook County Hospital on July 17, 1951, with the complaints of left lower abdominal pain, fainting, and a constant urge to defecate. Her last menstrual period had occurred on May 27, 1951, and she had bled slightly for one day at the time of her next expected menstrual

period. Present symptoms began on the day prior to her admission, and were associated with pelvic pressure and spotting. Her past history showed two previous normal spontaneous deliveries and a diagnosis of "pus tubes" in 1948.

The blood pressure was 118/76, pulse 88 per minute, and temperature normal. The patient did not appear acutely ill. The abdomen was obese and distended, and there were tenderness and rebound tenderness over the entire lower abdomen. Vaginal examination showed a slightly enlarged soft uterus with tenderness in the region of the left adnexa, but no palpable mass. The cervix was soft, bluish, closed, and pointed down and posteriorly. Motion of the cervix caused pain in the left adnexal region. The cul-de-sac was bulging. The hemoglobin was within normal limits.

On colpocentesis dark nonclotting blood was obtained, and laparotomy revealed a left tubal abortion with approximately 200 ml. of free blood and some clots in the peritoneal cavity. The right tube and ovary were normal, the latter containing a corpus luteum. A left salpingo-oophorectomy was performed, and the pathological report showed ectopic pregnancy of the left tube.

The patient returned twelve weeks later with a history of gradually enlarging abdomen and quickening on Oct. 7, 1951. Examination showed the uterus to be enlarged to the size of an 18 weeks' gestation. The intrauterine pregnancy continued uneventfully, and the patient was delivered, without complications, of a full-term 6 pound, 10 ounce, normal female infant on Feb. 28, 1952.

Review of Case Reports Since 1948

From a review of 68 cases in the world literature combined with our own 3 cases, the following statistical and clinical data were obtained:

Age and Parity.—In these 71 cases, the age of 63 patients was known, their average age being 30.9 years. Thirty-two patients (45 per cent) were 31 years old or over. This tendency toward the occurrence of combined pregnancy in the older age group has been previously reported.[1]

In the series reviewed 43 patients (60.6 per cent) were multiparas, 14 (19.7 per cent) were primiparas, and in 14 cases (19.7 per cent) the parity was not known.

Site of Ectopic Pregnancy

Of the 71 cases of combined pregnancy 59 ectopic gestations were known to occur in the tube. Thirty-three of these were in the right tube, 25 in the left tube, and one was bilateral.[21] Two of the tubal pregnancies were twin pregnancies in the tube in addition to the intrauterine gestation.[12, 21] In two cases, the site was not stated.[10] This predilection for the right tube is similar to the incidence found in single ectopic pregnancy.[3] There were 9 abdominal pregnancies[9, 18, 20, 22, 29, 32, 43, 48, 50] and one which was known to have arisen in the ovary.[36] The relatively large number of abdominal pregnancies is certainly accounted for by the fact that practically all cases of abdominouterine combined pregnancies will find their way into the literature.

TABLE I. SEQUENCE OF PROCEDURES

Group A	Cases in which the extrauterine pregnancy was terminated first	44 cases	(62.0%)
Group B	Cases in which the intrauterine pregnancy was terminated first by abortion or curettage	16 cases	(22.6%)
Group C	Cases in which the intrauterine pregnancy was terminated first by vaginal delivery or cesarean section.	10 cases	(14.0%)
Group D	Death without operation	1 case	(1.4%)
Total		71 cases	(100.0%)

Sequence of Procedures.—In 44 cases (62 per cent) the symptoms of an acute abdominal crisis caused by the ectopic pregnancy led to a laparotomy as the initial procedure, although the preoperative diagnosis of ectopic pregnancy was frequently missed (Group A). In 26 instances (36.6 per cent) the

intrauterine pregnancy terminated first, 16 times by spontaneous abortion or curettage (Group B), and ten times by vaginal delivery or cesarean section in cases which reached the third trimester (Group C). One patient,[31] known to be pregnant died of a cerebral hemorrhage before attempts at diagnosis could be made (Group D), and the case is included in this study because autopsy disclosed a combined pregnancy (Table I).

Diagnostic Accuracy

Before the termination of either pregnancy a correct diagnosis of combined pregnancy was made, or earnestly considered, in only 7 cases (9.9 per cent),[11, 15, 21, 23, 24, 47] all of them in Group A. In this group the uterine pregnancy was overlooked 26 times and all symptoms attributed to the ectopic gestation. In 10 other cases in this group an intrauterine pregnancy alone was diagnosed, and other indications for surgical intervention were given preoperatively. In one remaining instance in Group A, the pregnancy was not diagnosed at all,[8] and the patient was operated upon for acute appendicitis. In 15 of these cases the diagnosis of intrauterine pregnancy was not made, or was erroneously discarded following the discovery of an ectopic pregnancy at the time of laparotomy.

In Group B no correct diagnosis was made prior to the termination of the first pregnancy, and 8 of these were still left undiagnosed following this procedure. The elapsed time before laparotomy varied from a few hours to as much as 8 weeks, averaging 23 days.

The presence of a full-term or near-term ectopic gestation in 9 of the 10 cases in Group C was unrecognized prior to delivery of the intrauterine fetus. In the tenth case, a missed tubal abortion associated with an intrauterine gestation in the third trimester was also overlooked.[26] In 5 of these cases, operation was delayed as long as 2 to 8 weeks before the abdominal pregnancy was recognized.[18, 20, 32, 43, 48]

Summarizing, only 7 cases (9.9 per cent) were diagnosed correctly prior to the termination of either pregnancy, and 28 cases (39.4 per cent) still remained undiagnosed immediately following the termination of one pregnancy (Table II).

TABLE II. DIAGNOSTIC ACCURACY

	GROUP				TOTAL	%
	A	B	C	D		
Number of cases	44	16	10	1	71	
Recognized before the termination of the first pregnancy						
Both pregnancies	7	–	–	–	7	9.8
Intrauterine pregnancy	10	16	10	–	36	50.8
Ectopic pregnancy	26	–	–	1	27	38.0
No pregnancy	1	–	–	–	1	1.4
Second pregnancy still undiagnosed after termination of the first	15	8	5	–	28	39.4

TABLE III. DURATION OF PREGNANCIES

	TRIMESTER		
	FIRST	SECOND	THIRD
Group A.—			
Time of termination of ectopic pregnancy	41*	3	0
Time of termination of uterine pregnancy	10	9*	25
Groups B and C.—			
Time of termination of ectopic pregnancy	12*	4	10
Time of termination of uterine pregnancy	16	0	10*

*Case of triplets.

Duration of Pregnancies.—The estimation of the length of gestation was based upon the available data regarding the last menstrual period and the size of the fetus obtained. It appears signicant that the majority of pregnancies were terminated prior to 14 weeks' gestation, or, having reached that point, most often continued beyond 32 weeks' gestation. The length of gestation in the various groups appears in Table III.

Maternal Mortality.—There was only one maternal death[31] in this series of 71 cases (1.41 per cent). The death was nonobstetrical, due to a cerebrovascular accident during the sixth month of gestation in a 32-year-old patient who was hospitalized for an extrauterine pregnancy, but combined pregnancy was unsuspected.

Fetal Salvage.—Incomplete documentation makes it impossible to ascertain the fetal outcome in several cases. Four sets of triplets were encountered in this series, intrauterine twins with an ectopic pregnancy in 2 cases[7, 26] and 2 cases of a single uterine pregnancy with bilateral tubal pregnancy in one case,[21] and twins in a single tube in the other case.[12] Thus a total of 146 fetuses was present in the whole series. There were 43 infants known to have been born alive (29.5 per cent) of whom 7 were known to have died within the first week of life.

Of the 73 extrauterine fetuses, 7 were born alive (9.59 per cent).[9, 18, 20, 22, 29, 32, 43] Only four of these infants were known to have survived the first week of life, a fetal salvage rate of 5.48 per cent.[20, 22, 29, 32]

There were 73 intrauterine fetuses, of which 36 were known to have been born alive (49.3 per cent), 27 in Group A and 9 in Group C. Four of these failed to survive the first week of life,[7, 18, 41] reducing the fetal salvage rate to 43.8 per cent. The over-all salvage rate after one week of life was thus reduced to 24.7 per cent (Table IV).

TABLE IV. FETAL SALVAGE

	TOTAL	SURVIVED BIRTH		SURVIVED 1 WEEK	
Intrauterine infants	73	36	49.3%	32	43.8%
Extrauterine infants	73	7	9.5%	4	5.48%
Total infants	146	43	29.5%	36	24.7%

Comment

A most striking fact in this review is the infrequency with which the correct diagnosis was made. It is noted that of 71 cases an accurate diagnosis was made in only 7 cases prior to any terminating procedure. It is further noted that too frequently the presence of a second coexisting pregnancy was overlooked even after circumstances removed the first. This indicates the necessity for more thorough evaluation of these cases.

The diagnosis can be made more often if the condition is constantly borne in mind. The finding of an intrauterine pregnancy does not preclude the possibility of a coexisting extrauterine pregnancy, and, conversely, the finding of an ectopic gestation should not lead the physician to discard a previously made diagnosis of an intrauterine pregnancy too readily. Unilateral pain in a threatened abortion should always be viewed with suspicion, and careful bimanual examination before curettage and the judicious employment of procedures such as colpocentesis, colpotomy, culdoscopy and x-ray visualization when indicated can aid in the diagnosis of a possible ectopic pregnancy. Too often the differential diagnosis in a questionable case is apparently resolved

by the findings of placental tissue or fetal parts in the uterine cavity, and further search is ended. Similarly, when the signs and symptoms clearly point to a diagnosis of ectopic pregnancy, a slightly enlarged uterus might easily be mistaken for consensual hypertrophy and an intrauterine pregnancy thereby overlooked. In this group, metrorrhagia is an unreliable sign, since the presence of an intact intrauterine pregnancy decreases the likelihood of external bleeding.

Past reviews[1] have shown that the prognosis has been better for the mother and fetus in the cases in which the initial symptoms were caused by the ectopic pregnancy, even though the intrauterine gestation often was overlooked, since the more serious aspect of the condition had been removed. In the cases in which the ectopic pregnancy remained undiagnosed, the morbidity often was extended for days or even weeks. And, though no deaths were reported as a result, the extent of permanent damage would be difficult to estimate.

The lives of the mother and fetus depend to a great degree on the treatment of the extrauterine aspect of this condition. On vaginal examination prior to laparotomy, a closed cervix, minimal vaginal bleeding, and the presence of a slightly enlarged and soft uterus should warn the surgeon against the possibility of disturbing an intact intrauterine pregnancy. Should the cervix show partial dilation, however, or if the bleeding has been brisk, evacuation of the uterus, at this time, seems advisable. The treatment of the ectopic pregnancy is surgical whenever it is recognized, regardless of the presence of the intrauterine gestation, except in cases nearing viability where salvage of the abdominal pregnancy might warrant consideration. In the cases in which salpingectomy is performed early, postoperative care should be directed toward maintaining the intrauterine pregnancy. The free use of blood, fluids, hormones, and antibiotics is important in the proper postoperative care.

An interesting aspect of combined pregnancy, which we have previously referred to, bears further mention at this time. It has been previously shown that a large majority of combined pregnancies do not continue beyond the first trimester.[9] In the cases where both pregnancies do continue beyond that point, however, a large percentage reach viability, and often result in two viable births.[22] The increased incidence of continuation of the extrauterine pregnancy to term under these conditions may be explained on the basis of a better pelvic blood supply in conjunction with the intrauterine pregnancy.[4] In the management of these cases, the intrauterine pregnancy may be allowed to terminate first, followed by laparotomy for the abdominal pregnancy.[43]

With the advent of improved surgical and diagnostic techniques, ready accessibility of blood, and the use of antibiotics, the maternal mortality has dropped from previously reported rates[1] of 14.4 to 19 per cent in 1940, to a rate of slightly over 1 per cent. The only death reported in this series was nonobstetrical. The maternal morbidity, however, remains high, especially in cases in which the ectopic pregnancy is overlooked.

Reports[1] have indicated the fetal salvage from the uterine pregnancy as varying from 54 per cent down to 35 per cent. The usual survival rate of the extrauterine fetus has been given as 5 to slightly over 15 per cent.[32] Of the

latter, however, no more than half survived the first week of neonatal life. In this review there were 36 fetuses salvaged out of a total of 73 intrauterine fetuses, a rate of 49.3 per cent; of the 73 extrauterine fetuses, only 7 survived, a salvage rate of 9.5 per cent. After the first week of neonatal life these rates were reduced to 43.8 and 5.48 per cent, respectively.

Summary

1. Combined intra- and extrauterine pregnancy is an infrequent clinical entity. The literature has been reviewed, and to the critical analysis of 395 cases of combined pregnancy by DeVoe and Pratt in 1948 3 cases of our own and an additional 68 cases from the world literature up to Dec. 31, 1954, have been added. The entity has been estimated to occur approximately once in 30,000 pregnancies.

2. In the 71 cases reviewed the correct diagnosis was made only 7 times (9.9 per cent). In approximately 40 per cent of the cases, the presence of a second pregnancy was overlooked, even after removal or termination of the first.

3. The failure to recognize the coexistence of the 2 pregnancies can lead to increased maternal morbidity and may jeopardize the life of the mother. The morbidity was highest in cases in which the extrauterine aspect of the condition was overlooked.

4. The diagnosis can be made more often if the possibility of this syndrome is borne in mind. In the presence of conflicting signs and symptoms, errors may be avoided by the employment of all available diagnostic procedures.

5. Most combined pregnancies terminate in the first or third trimester. In the presence of an intrauterine pregnancy, the chance of continuation of the ectopic pregnancy is greatly increased.

6. When a diagnosis of an extrauterine pregnancy is made, the treatment is surgical. The management of the uterine pregnancy is conservative unless abortion is inevitable or spontaneous.

7. Fetal salvage can be improved if the management is directed toward maintaining the intrauterine pregnancy by: (a) avoiding curettage in the presence of a closed cervix and minimal bleeding, and (b) adequate postoperative therapy following laparotomy.

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Discussion

DR. FREDERICK J. HOFMEISTER, Milwaukee, Wis.—I believe that one of the cases listed in the 68 is mine. I want to call attention to one detail, the difficulty of diagnosis. It is not quite as easy as it might seem. The presence of a unilateral swelling coexistent with an intrauterine pregnancy should alert one to the possibility of an ovarian cyst or an ectopic pregnancy. Cautious observation should be the pattern of attack. Many abdomens will be opened unnecessarily if the presence of unilateral swelling and pain coexistent with intrauterine pregnancy is always interpreted as an ectopic pregnancy. It is essential to remember that observation to the fourth month will often show that the ovary associated with normal pregnancy can remain extremely large and suddenly virtually disappear with the spontaneous regression of the cystic corpus luteum. This in our own experience has resulted in the necessity of cancelling a prospective operation on patients who were being observed as having a possible ovarian cyst coexistent with normal pregnancy.

In our case of combined intra- and extrauterine pregnancy, we were aware of this unilateral enlargement and thought it to be a cystic corpus luteum. At about the third month of gestation, the patient reported sudden lower abdominal pain. When she entered the hospital, she practically made the diagnosis of ruptured ectopic pregnancy by stating that she was unable to lie flat because of subdiaphragmatic pain. Examination showed enlargement of the uterus consistent with the period of amenorrhea. The right adnexal area was extremely tender. A preoperative diagnosis of intrauterine pregnancy and ruptured ectopic pregnancy was established. Laparotomy confirmed the preoperative diagnosis.

CLOSURE OF THE HUMAN PALATE IN EMBRYO

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THIS study attempts a more precise determination of the normal time range in which closure of the human palate takes place. It presents graphically, in Fig. 1, the state of palatal closure in 60 embryos according to crown-rump lengths (*CRL*) and, in 49 of these embryos according to estimated ovulation ages (*OA*). The degree of association between these two variables is also shown. The data yield a clearer picture than was available before regarding the active range of closure of the palate and, in addition, offer a convenient base to which can be added comparable data from other sources.

Background

Much current literature stresses the possibility that untoward environmental agents or conditions, acting during pregnancy, may cause cleft palate in humans. Clearly, it is important to consider the stage of gestation during which the presumed injury to the embryo occurs. There is no evidence that the palatal processes of the maxilla ever reopen, once they have fused. Therefore, any environmental factor which might arrest palatal closure, or which might increase the chance that a moderate genetic deficiency in facial growth rate may be expressed in cleft palate, must act before closure has occurred. Thus it is of both practical and theoretical consequence to learn, as accurately as possible, when closure of the human palate takes place.

Aside from carefully timed experiments with primates, the only approach to the problem that is presently available is the study of specimens in existing collections of human embryos. Individual differences in the time of palatal closure must be anticipated because variations in rates of structural development have been found for all organs studied systematically. It is thus desirable to study, not merely a few cases, but a substantial number of embryos.

Methods

With these considerations in mind, 77 embryos were examined at the Department of Embryology, Carnegie Institution of Washington. In addition, 5 embryos were examined at the University of Minnesota, 3 at the University of Illinois, and 3 at Western Reserve University. The Carnegie material used in this study was catalogued as normal. On the basis of good records, Western Reserve's 3 embryos could also be judged as normal. No histories were available for the embryos from the other universities.

The study was made by microscopic examination of all human embryos of the pertinent sizes that were available in these collections, so far as could be learned, in 1955. Frontal and transverse sections were obtained of embryos ranging from 16 to 50 mm. crown-rump length. Each embryo was examined systematically through the entire head region. Space, if any, between the palatal processes was measured in millimeters on the Edinger projector at ×100. These measurements were made at 5 points along the palatal plane: at the extreme anterior and posterior ends, and at 3 equidistant locations in between.

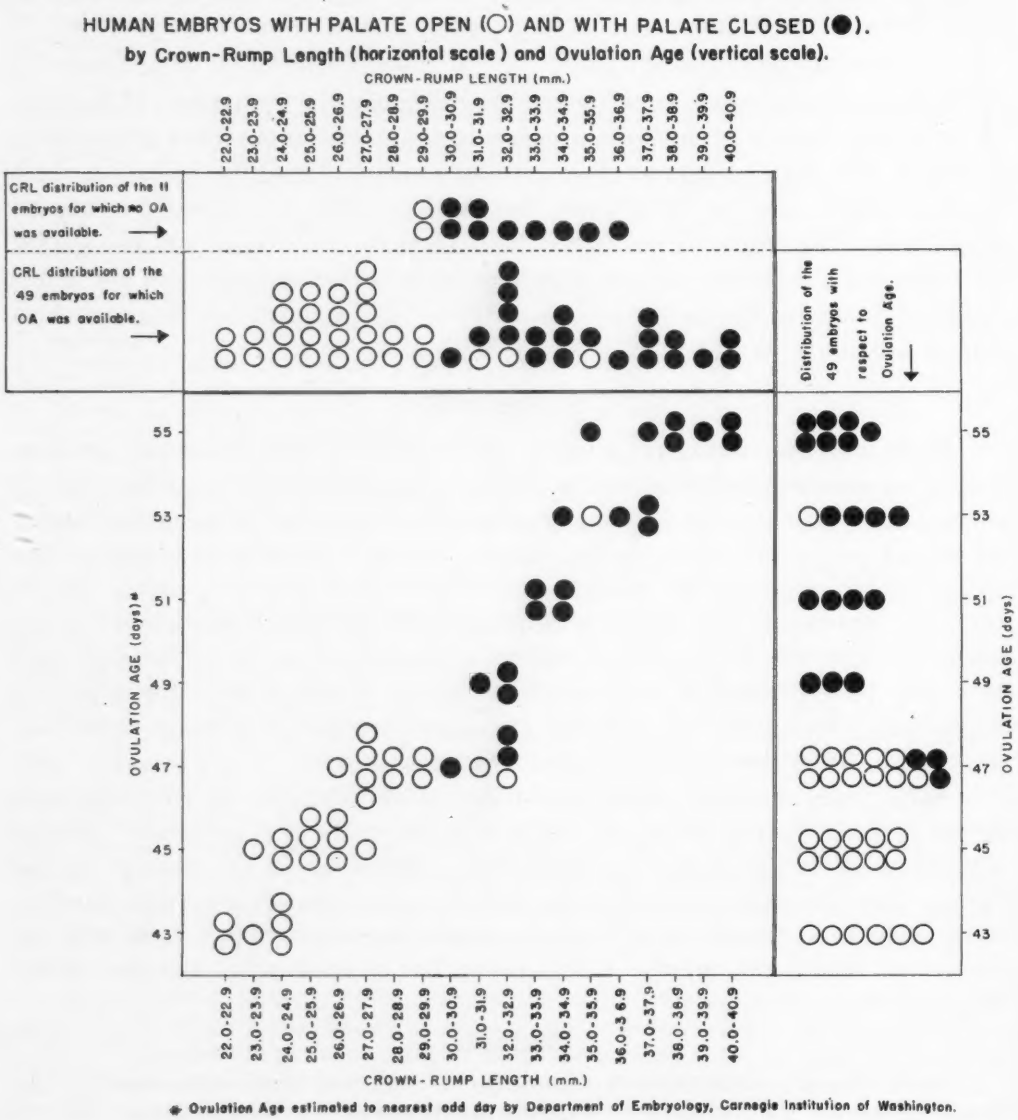

Fig. 1.

A preliminary plotting of the 88 embryos according to crown-rump length showed that the critical period for palatal closure was not far from 30 mm. It was clear that the extreme cases in the distribution contributed no statistical

information. The distribution to be considered was therefore shortened to cover the range between 22 and 41 mm. crown-rump length. This range included 60 embryos.

Aside from crown-rump length, two other indicators of embryonic age were considered. Menstruation age (date of onset of last menses) was available for 36 of the embryos. Ovulation age had been judged for 30 of the embryos by Streeter, Heuser, and Corner[1] in studies of developmental "horizons." For the remaining 19 embryos at Carnegie, ovulation age was estimated by fitting them to an extension of Streeter's curve.

Findings

When scatter plots, representing the three possible interrelations among menstruation age, ovulation age, and crown-rump length were set up and examined, it was obvious that no association of consequence existed between menstruation age and either of the other variables. This is not altogether surprising, considering the fact that, although these embryos were morphologically normal, they were all early pregnancy terminations. The circumstances under which these conceptuses were obtained are probably not conducive to accurate ascertainment of menstruation age.

As seen in Fig. 1, the association between crown-rump length and ovulation age is marked. Indeed, the fact that this association is so high suggests that crown-rump length and variables associated with it received, perhaps necessarily, strong weighting in judging ovulation age. However, the "horizon" studies[1] gave detailed consideration to the developmental status of key organs of the embryo, rating them on a system of point scores for purposes of classifying the embryos in terms of the "horizon" categories. From a statistical viewpoint it is unfortunate that the judges used rather coarse groupings, viz., to the nearest odd day, rather than to the nearest single day of estimated ovulation age, but it should be stressed that this factor does not significantly affect the general validity of the judgments made.

It appears that the threshold period of palatal closure lies between 29 and 33 mm. of crown-rump length and between 47 and 49 days of ovulation age. For the purposes of this study the embryonic palates were considered closed if the converging maxillary processes were touching at any place along the palatal plane. It was assumed that, once any part of the processes had met, closure along the length of the palate would have proceeded in rapid and orderly fashion if gestation had continued.

Table I lists the 5 measurements along the palatal plane of the 10 Carnegie embryos which are found in the critical range. In these cases the palate closes in what Hochstetter[2] has called an X configuration: first, at a point distal to the anterior end (equaling a fourth of the entire length), continues back through the middle half, then closes through the anterior fourth, and finally through the posterior fourth.

With a single exception, the hard palates were completely closed in all embryos greater than 33 mm. crown-rump length. The soft palate varied from an opening of 0.3 mm. to a slight notch. The exception, an embryo of 35 mm. crown-rump length and 53 days' ovulation age, was in transverse section through the head region and it was difficult to find the exact level of the palate. At the approximate level the palate seemed to be open although the distance was too small to measure and could have been an artifact.

All of the embryos below 29 mm. crown-rump length had the maxillary palatal processes in a vertical position, the distance between them averaging 1.50 mm. In these cases, the tongue was found between the vertical processes

and extending upward almost to the lower border of the nasal septum. In the two 29 mm. embryos, however, the maxillary processes were horizontal with the tongue beneath. Their measurements are given in Table I.

TABLE I. CLOSURE OF THE PALATE IN HUMAN EMBRYOS
Measurements of the opening in the palate at five equidistant points

EMBRYO	CRL (MM.)	ANTERIOR END (MM.)	POINT 1 (MM.)	POINT 2 (MM.)	POINT 3 (MM.)	POSTERIOR END (MM.)
950	29.0	.45	.27	.36	.47	.54
4205	29.5	.23	.15	.20	.35	.41
4570	30.7	.42	Closed	Closed	Closed	.37
9226	31.0	.26	Closed	Closed	Closed	.06
6573	31.5	.22	.01	.08	.14	.49
417	32.0	.03	Closed	.03	.28	.95
5154	32.0	.04	.03	.01	.01	.02
609	32.0	.20	Closed	Closed	Closed	Closed
4289	32.2	.17	Closed	.05	.15	.41
1153	32.3	Closed	Closed	Closed	Closed	Notched

It would be very desirable to add more cases to those now available. When, or if, there are about two dozen cases for each interval of crown-rump length (1 mm. per interval), it will be appropriate to compute the percentage of embryos in each interval that have the palate closed. This will probably vary, according to present indications, from 0 at around 28 mm. to 100 at around 36 mm. When the values representing per cents with palate closed are connected by a smoothed curve, it will be easy to locate the crown-rump length where the curve reaches 50 per cent, and this crown-rump length may be taken as the best estimate of the average stage, in crown-rump length units, when the palate closes.

In the meantime, it is to be hoped that more knowledge will accumulate on the relation between crown-rump length and true ovulation age, so that translation of the findings into practical terms (menstruation age) can be accomplished with greater accuracy than our present knowledge allows.

Conclusion

From the cases already studied it seems safe to say that the human palate closes at about the end of the seventh week of ovulation age, or near the end of the ninth week of gestation as reckoned from onset of last menses. Thus any untoward environmental agent or condition which may cause failure of palatal closure, or which may increase the chance that a moderate genetic deficiency in facial growth rate will be expressed in cleft palate, must act well before the end of the first trimester of pregnancy.

Sincere thanks are due the following for making material and facilities available: Dr. George W. Corner and the staff of the Carnegie Institution, Dr. Lemen Wells, University of Minnesota, Dr. Arnold A. Zimmerman, University of Illinois, and Dr. Samuel W. Chase, Western Reserve University.

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Editorial

II. FURTHER THOUGHTS ON THE QUESTIONNAIRE OBJECTIVES OF THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

In a recent Editorial, the principal results of the questionnaire answered by over 4,000 subscribers of the JOURNAL were reported. Although some general comments were made on these tabulated opinions, there appears to be a need, in the light of the replies to the questionnaire, for an editorial in regard to the objectives of the JOURNAL. Dispensing with any attempt to find a general, and probably sententious statement, we should like to comment on a number of functions or departments of the JOURNAL.

1. *For the reader* the JOURNAL tries to provide for the most part "original articles" reporting on work actually done in laboratory or hospital by investigators interested in the field. The JOURNAL recognizes the need for "symposia" or "review articles" and will endeavor to supply a certain number of these, but the Editors believe that the presentation of such abstracted and digested material is not its primary function.

It is not expected that all subscribers will read all of the JOURNAL. The reading of the JOURNAL should not be regarded as a passive process. Rather, the reader must choose from the material presented that of special interest to him, and discard that which he considers irrelevant to his work or perhaps what he may regard as worthless. The Editors *certainly do not arrogate to themselves* the right to decide finally what obstetricians and gynecologists shall read, but rather to present for consideration what they believe to be honest reports of well-controlled investigations. From these, the reader must make for himself some effort at selection.

2. *The contributor's position* was not considered in the questionnaire, although the responsibility of the JOURNAL to him is not less than to the reader. Furthermore, the interests of reader and contributor are not necessarily identical.

The contributor, whether from hospital or laboratory, has as one of his requirements that data be published in detail sufficient to enable other investigators primarily interested in the field to convince themselves of the validity of his conclusions. It is further necessary that future investigators be spared the labor of repetition. Thus many articles may contain what appear to the general reader to be unnecessary tables or statistics, but to those working in the same field such data may be entirely essential. *The* JOURNAL *is a repository to facilitate the exchange of information necessary for medical purposes.* These considerations should be borne in mind by the reader, impatient over pages of what, to him, seem uninteresting and unnecessary data.

The contributor deserves also a reasonable freedom in his use of words, manner of expression, and mode of presentation. The Editors use their influence, and occasionally their authority, in favor of clarity, brevity, and the use of the English language. Articles cannot be completely rewritten, however, and the Editors are often faced with the dilemma of rejecting or accepting an article which they deem a contribution to knowledge, but which they believe could have been better presented.

3. The publication of papers read before certain major obstetrical and gynecological societies also seems to the Editors of importance, since the total of the papers read before such societies gives an excellent general view of the problems facing the profession and specialty at a given time. These transactions in their published form represent *a chronicle of obstetrical and gynecological progress.*

The papers read before these major societies are in general of a high order. Admittedly, a few papers are below the JOURNAL'S standards, and yet appear in print. Once again the Editors want to point out that they do not wish to serve as the exclusive arbiters of what the American obstetrician and gynecologist shall read. All papers submitted by special societies are approved by the societies and so recommended for publication. The Editors reserve the right to question or decline papers that are careless or inept, but believe that the societies carry a major responsibility in what they submit for publication. The considered opinion of the publications committee of a society that a paper deserves publication should then be given appropriate weight.

4. The publication of Case Reports has been under some criticism for many years and was commented upon unfavorably by many of those who answered the questionnaire. Yet the Editors believe there remains a place for the "Case Report," and for a variety of reasons.

Medical teaching has traditionally been based on the case system, as has the teaching of the law and other professional disciplines. The use of generalizations based on statistics is a recent device and certainly cannot replace the older method, at least for all types of intelligence. Besides being an alternative method of approach, the publication of the isolated case report, in the instance of the rare condition or unusual occurrence, is perhaps the first step in what may some day be a statistical synthesis based on the collection of published reports of isolated cases.

With these words in favor of the case report, the Editors must warn that such cases, to be accepted as reports, must be so unusual as to preclude the possibility of a "series of cases" and must be tersely and clearly described.

The section devoted to Correspondence also received many disapproving notes, and yet this department is scarcely to be dispensed with. Space must be available to those who wish to take exception to statements made in published articles, to assert, if they wish, that their own work has been misquoted or not recognized as having priority. The Editors wish that such letters were more numerous, much briefer, and perhaps more acrimonious.

There were a few critics of the policy of publishing articles from abroad. Actually, if papers originating in Canada are excluded, such articles have comprised in the last year only about 2.5 per cent of the papers published and the rejection rate is appreciably higher than for articles originating in the United States.

It appears to us a courtesy, and a minor contribution to American foreign relations, to consider papers emanating from abroad. Medical science certainly should have no national boundaries. Furthermore, it is our impression that at least a portion of the foreign articles provide a different point of view which may be stimulating after the first minor shock is over. We expect to receive for consideration more articles from abroad, on topics which provide a valuable contrast with conditions or procedures familiar to the American scene.

These comments on particular aspects of the JOURNAL'S function provide the basis for formulating its objectives. First of all, it must be remembered that reader and contributor both have their claims upon us.

For the reader, it is our aim to supply the best of the original articles that are sent to us, but we do not think it is possible to print only articles of universal interest, or to prepare material that can be lightly read without study.

For the contributor, we believe we must permit reasonable latitude in expression, and reasonable space for the presentation of data that he regards as essential for the documentation of his conclusions, and as a basis for the further development of the subject by other workers.

W. J. D.
H. C. T.

Case Reports, New Instruments and Methods

POSTURE REQUIREMENTS OF THE NEWBORN INFANT

ALLAN BLOXSOM, M.D., HOUSTON, TEXAS

THE newborn infant, soon after delivery and start of respiration, is placed in an incubator or crib. There he continues to go through the major transitions of (a) extrauterine respiration, and (b) changing from fetal to adult type of cardiac circulation that take place only at this time of life. For the nurse and physician the placing of the infant in an incubator or crib is one of the easiest and outwardly simplest things to do at this time for the newborn infant. Because it is such an easy and natural thing to do, less thought has been devoted to positioning the newborn infant than to any other treatment given or ordered in this period.

In the immediate newborn period the major transitions in respiration and in cardiac circulation take place. The occurrence of mucus with its frequently sudden onset a few hours after birth, the altered respirations seen in hyaline membrane disease also a few hours after birth, the left ventricular hypertrophy beginning immediately with the increased cardiac work load and continuing for a period of several weeks to months following birth, and the occasional periods of cyanosis are clinical evidence in the following few hours after delivery of the transitions in respiration and in cardiac circulation peculiar only to the newborn infant.

I[1] have called attention to the occurrence of mucus in the newborn infant treated in the Air Lock, finding that it occurs in approximately 12 per cent of term infants and 30 per cent of premature infants. Smith[2] mentioned the rapid left ventricular hypertrophy that occurs after birth during the first few weeks to months, indicating the increased work load on this side of the heart imposed by the increased muscle tone and demands of a comparatively great body surface.

The recent M & R conference on pulmonary hyaline membranes[3] attests the importance of this condition seen chiefly in the premature infant and the infant delivered by cesarean section.

Lendrum[4] has recommended that the positions and handling of the newborn premature infant be planned with the object of avoiding overload in the thoracic veins and pulmonary circulation to avoid if possible congestive pulmonary failure that might lead to hyaline membrane disease. He recommends that the position of the newborn infant during the first 48 hours of extrauterine life be such that any excess of venous blood would accumulate below the diaphragm and not above the diaphragm.

To cushion the immediate effects of birth as much as possible, the newborn infant should be positioned so as to:

1. Maintain the physiological flexion of the spine started in intrauterine life.

2. Maintain an open airway by placing the head down so that the tongue can fall forward.

3. Provide a down gradient for the flow of mucus from the throat to the mouth.

4. Maintain the weight of the liver, spleen, and other abdominal organs lower than the thorax for an increased pulmonary expansion.

5. Minimize the immediate increased work load on the left ventricle by providing a down gradient for the flow of blood to the systemic circulation.

6. Provide a cisternal space for the excess blood in the abdominal cavity through a pendent position of the abdomen after ligation of the umbilical cord.

7. Minimize the overload in the thoracic veins and pulmonary circulation by having the venous blood maintained by gravity below the diaphragm.

A clear Plexiglas contour cradle has been devised and molded as shown in Fig. 1.

Fig. 1.

This cradle is of sufficiently small size and light weight that it can be carried and placed in any crib, incubator, or Air Lock. Upon it the newborn infant can be positioned on his abdomen during the first few days of life after delivery. At regular intervals the infant can be removed for feeding and body care.

Fig. 2 shows a manikin on this contour cradle, and the method of holding an infant to the cradle through diapers when on rocking mechanism.

Seventeen consecutive normal newborn infants have been placed in a prone position on this contour cradle. Respiratory and cardiac rates have been taken every 2 hours for the first 48 hours after delivery.

The contour cradle enables the head to fall forward to position the face to either side, the thorax to be maintained horizontally in the highest plane of the infant's body, the abdomen with its blood vessels to hang below the

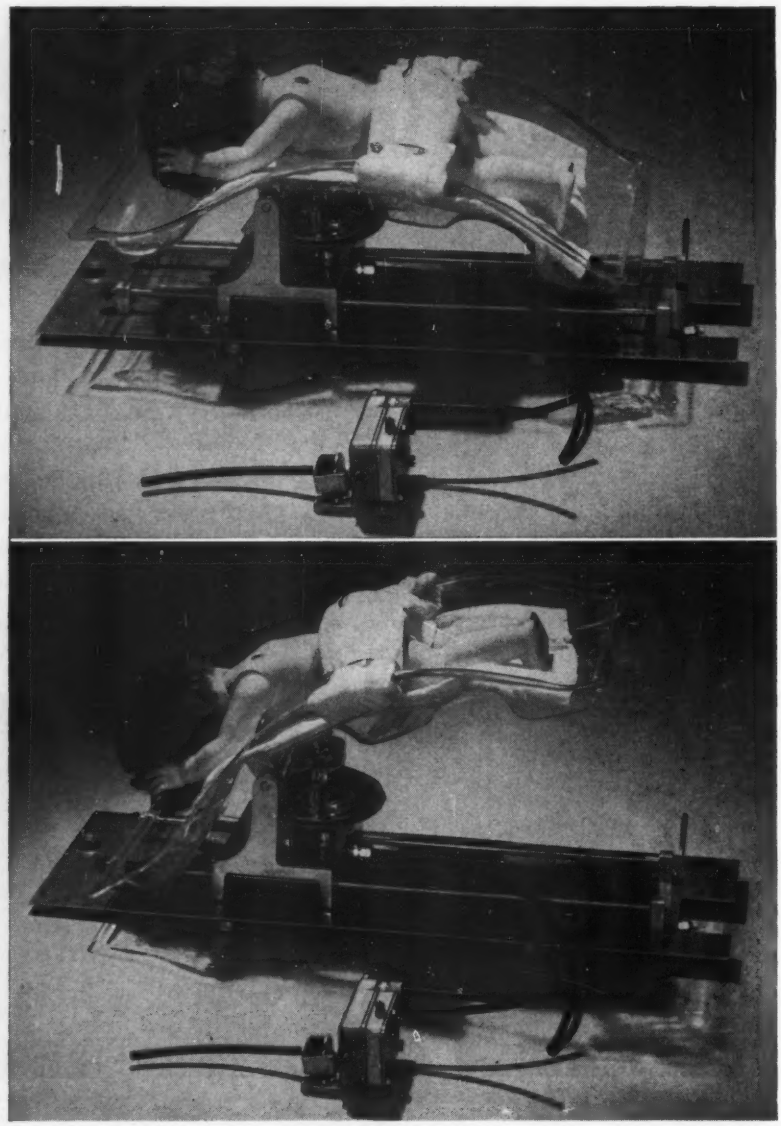

Fig. 2.

level of the diaphragm, the abdomen to place no weight upon the umbilicus, the lower extremities to be below the level of the abdomen, and the spine to be in a normal physiological flexed position found before delivery.

Infants maintained in this physiological position have been remarkably comfortable, and in a small series have developed very few of the undesirable symptoms seen in the immediate newborn period. It must be stressed that so

far the series has been too small to state the extent to which the immediate undesirable clinical symptoms will be reduced in the infants so physiologically positioned, but it is logical to assume from a theoretical point that such difficulties will be minimal and unavoidable.

The only theoretical criticism of the physiological position of the infant immediately after delivery is that if the cord is not adequately tied hemorrhage might occur more easily. This is offset by the fact that should any bleeding occur from a faultily tied cord it will stand out like a red flag through the clear plastic cradle and be apparent immediately to the nurse on duty. This is not discovered by the nurse observing the infant in an ordinary crib or incubator unless she happens to turn the infant over.

Summary

A clear Plexiglas contour cradle has been devised to position the newborn infant physiologically so as to maintain a normal flexion of the spine, a lowered position of the head to maintain an open airway and allow mucus to escape, a lowered position of the liver and spleen to help maintain pulmonary expansion, and a lowered pendent position of the abdomen with its vessels to act as a cisternal reservoir to keep blood that might accumulate as an excess below the level of the diaphragm.

The contour cradle places no weight upon the umbilicus or abdomen, and should any bleeding occur from a faultily tied cord the spotting acts as a red flag and can be seen at once by the nurse on duty.

The contour cradle may be used in any incubator or crib on a pneumatic rocking mechanism.

Respiratory rates and pulse rates of 17 consecutive newborn normal term infants showed a steep fall during the 48 hour period these infants were on the contour cradle in a prone position. It is believed that when a normal newborn infant is placed on this cradle a more efficient and rapid pulmonary expansion occurs.

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SHEEHAN'S SYNDROME FOLLOWING PROVED AND TREATED AFIBRINOGENEMIA*

A Case Report

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POSTPARTUM hemorrhage and shock have been described preceding the development of postpartum panhypopituitarism. Simmonds,[1] in 1914, repeatedly found pituitary infarcts in women who died of puerperal sepsis. Sheehan[2, 3, 4] in a series of papers beginning in 1937 greatly clarified this subject. From observations made in a large maternity hospital in Glasgow, he showed that areas of pituitary necrosis of varying size are commonly found in women who die during the puerperium after a delivery associated with postpartum hemorrhage. He was satisfied that infarction was due to marked ischemia of the pituitary with resultant necrosis. A recent monograph by Farquharson[5] gives an excellent discussion of the clinical aspects of insufficiency of the adenohypophysis following complications of pregnancy and other conditions.

Review of the literature, to the best of our knowledge, has failed to disclose any report of the development of Sheehan's syndrome following an episode of proved and successfully treated afibrinogenemia. The following case report, we feel, exemplifies such a chain of events.

Case Report

The patient, a 31-year-old white para ii-o-o-ii, made five visits to the prenatal clinic of the Jewish Hospital of Brooklyn, after the twentieth week of gestation. Her antepartum course and laboratory findings were within normal limits. At term the patient was admitted to the hospital at 10:30 P.M., on June 17, 1955, in early labor with mild contractions occurring every eight minutes. The cervix was effaced, 2 cm. dilated, and the vertex presented at minus one station. Fifteen minutes after admission, while the enema was being expelled, the membranes ruptured spontaneously and strong uterine contractions ensued at two- to three-minute intervals; the patient was now given sedation with Demerol, 50 mg., scopolamine, 0.2 mg., and Benadryl, 50 mg., intramuscularly. By 11:00 P.M. (one-half hour after admission) the cervix was 7 cm. dilated. At 11:10 P.M. a tetanic uterine contraction which lasted almost five minutes was noted, and the uterus seemed to be hypertonic until delivery at 11:20 P.M. During this ten-minute interval the patient was transferred to the delivery room, a pudendal block was performed with 50 c.c. of 1 per cent procaine, and, because of difficulty in obtaining the fetal heart tones, delivery was easily effected by low

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forceps under supplemental nitrous oxide-oxygen inhalation anesthesia. A moderately depressed 3,090 gram female infant, born with two tight loops of cord about the neck, responded to simple resuscitative measures within three minutes. The placenta was delivered spontaneously after a three-minute third stage and showed no abnormalities or evidences of premature separation. Methergine, 0.2 mg., was given intramuscularly at this time.

Ten minutes after delivery, or one hour after admission, when the fundus was apparently well contracted, a gush of blood and small clots, estimated at 300 c.c., issued forth from the birth canal. Pitocin was administered intramuscularly and by intravenous drip. Examination of the birth canal showed that the blood was coming from the uterine cavity. By midnight, 40 minutes following delivery, because vaginal bleeding persisted, though not at an alarming rate, blood was drawn for cross-match and clot observation. The test revealed a poor, friable clot which formed in 10 minutes. The blood pressure now had fallen from 120/90 to 96/60. Bleeding per vaginam persisted. At 12:30 A.M. blood replacement therapy was begun. From this time until 3:05 A.M. the patient received 500 c.c. of dextran, 2,500 c.c. of bank blood, 500 c.c. of fresh blood, 1,000 c.c. of 5 per cent glucose in distilled water, 500 c.c. of normal saline, and 8 Gm. of fibrinogen. The blood pressure now was 88/64 having risen from a low of 40/0 during the period of blood and fluid replacement. The bleeding from the vagina was now much less and clots were present. The patient's course had been followed by numerous clot observation tests. Blood drawn at 12:50 A.M. showed no evidence of clotting even after standing for eight hours, whereas blood drawn following the described therapy formed a stable clot in four minutes.

At about 4 A.M. uterine atony was observed, evidenced by a soft fundus and resumption of vaginal bleeding. The vaginal blood flow contained clots at this time. The uterine atony was successfully treated with an additional 1,000 c.c. of bank blood and intravenous Pitocin drip. By 6:05 A.M. the blood pressure was 118/70 and the vaginal bleeding had ceased.

An oxalated blood sample, drawn at 12:50 A.M., at the same time as the clot observation sample which did not clot in eight hours, was reported by the laboratory to contain less than 50 mg. per cent of fibrinogen. The blood fibrinogen level ten hours after delivery was 600 mg. per cent.

The eight-day postpartum hospital stay of the patient was uneventful except for fever on the first postpartum day. It was of further interest that there was a complete absence of lactation during the puerperium, despite the fact that following both previous pregnancies marked breast engorgement and discomfort had been encountered.

When seen in the postpartum clinic ten weeks following delivery, the patient had not yet resumed menstruation. In the ensuing nine months the patient complained of amenorrhea (except for slight staining for two days at three months post partum), absence of sweating, a dry, coarse skin, a weight gain of 15 pounds, general asthenia, partial loss of scalp, axillary, and pubic hair, dizziness, faint spells, and decreased libido. The patient's blood pressure varied between 70/40 and 90/70.

Certain laboratory data obtained during the patient's visits to the Endocrine Clinic are worthy of mention: 24 hour urinary estrin, negative and 1 to 2 rat units; endometrial biopsy showed simple proliferative hyperplasia; basal metabolism rate was minus 28 per cent; 17-hydroxycorticoids (including 11-oxysteroids) were 1.5 and 0.9 mg. per 24 hour urine specimen; the serum potassium was 6.26 milliequivalents per liter. The 17-ketosteroids, as well as the serum sodium and the glucose tolerance test, were within normal limits. X-rays of the sella turcica, likewise, were normal.

The clinical symptoms and pertinent abnormal laboratory findings are indicative of pituitary hypofunction involving the lactogenic, gonado-, thyro-, and adrenotrophic factors.

Comment

We have presented a case of tumultuous labor with resultant afibrinogenemia (possibly due to amniotic fluid infusion), leading in turn to hemorrhage, shock, and partial pituitary necrosis.

The postulated intravascular clotting following the amniotic fluid infusion may have partly occluded the pituitary sinusoids, the circulation in which must have been further markedly embarrassed by the progressive fall in blood pressure which followed delivery.

The danger of a subsequent pregnancy in a patient with Sheehan's syndrome was emphasized by Israel and Conston.[6] These authors reported a case of their own, and four others from the literature, in which pregnancy followed the development of Sheehan's syndrome. Symptomatic improvement was evident during the subsequent pregnancy in each case, yet all five patients died at delivery or in the puerperium in acute collapse. These sudden deaths were attributed to an inability of the previously impaired pituitary to supply the "acutely demanded corticotrophin, or the failure of the adrenals to secrete the essential corticoids,"[6] in response to a stress situation.

Summary

1. A case of Sheehan's syndrome following an episode of proved and successfully treated afibrinogenemia is reported.

2. The danger of rare subsequent pregnancy in such a case is mentioned.

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FULL-TERM INTRAUTERINE GESTATION AFTER SALPINGECTOMY AND SALPINGOSTOMY FOR TWO CONSECUTIVE ECTOPIC PREGNANCIES

A Case Report

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THE successful completion of an intrauterine gestation after ectopic pregnancies in both tubes is still a rare occurrence today. Stromme,[1] in 1953, presented the first case in the English literature of repeated ectopic pregnancies with salpingotomy followed by intrauterine gestation. A second similar case is herewith presented.

E. M., aged 29 years, was first seen by one of us (W. S.) in June, 1951. Her chief complaint was frequent and painful micturition. The menstrual history had been normal. In September, 1950, the patient had had a right salpingectomy for an ectopic pregnancy and appendectomy.

Urinalysis disclosed the presence of a yeast infection which responded promptly to treatment.

The patient was next seen in August, 1953, because of infertility. She offered no other complaints. On examination a small mass of about 2.5 to 3 cm. could be felt in the right adnexa.

On Nov. 8, 1953, the patient was admitted to the hospital with a history of 15 days of continuous vaginal bleeding and the passing of small clots. She complained of a sensation of fullness and tenderness in the left lower quadrant extending to the flank. Associated symptoms were headache, nausea, and fatigue. Pelvic examination showed a slightly boggy uterus and blood oozing from the external os. There was no cul-de-sac tenderness. A large mass about 5 cm. in diameter could be felt in the right adnexal area, and a tentative diagnosis of ovarian cyst was made.

A dilatation and curettage and a laparotomy were performed. It was noted that the right tube was missing. The right ovary was replaced by a cyst measuring 5 by 3.5 by 3.1 cm. which was removed. A wedge resection of the left ovary was done for multiple small cysts. Further inspection showed a nodule in the distal third of the left tube completely blocking the lumen. The tube was incised longitudinally, and the nodule was shelled out. The salpinx was then closed in two layers with interrupted No. 3-0 chromic catgut over a No. 12 soft rubber catheter which was removed at once after closing. The patient made an uneventful recovery and was discharged on the tenth postoperative day.

The pathological findings were of interest. The endometrium showed decidual reactions. The right ovary, measuring 5 by 3.5 by 3.1 cm., consisted of follicular and corpus luteum cysts. Microscopic examination of the nodule in the left tube showed a blood clot containing chorionic villi. The diagnosis was tubal pregnancy.

Following her discharge from the hospital, the patient became increasingly nervous and inconsolable about her inability to have children. At one time she committed herself to a psychiatric institution for fear that she would commit suicide.

A Rubin test was performed in September, 1954, and the tube was found to be open at 160 mm. Hg pressure. Following this, the patient had vaginal bleeding off and on for five weeks. The patient was again seen in May, 1955, reporting that her last normal menstruation had been on March 24, 1955. Examination disclosed a uterus corresponding to a pregnancy of about 2 to 3 months. The pregnancy progressed uneventfully. Because of a borderline pelvis a cesarean section was decided upon and she was delivered on Dec. 16, 1955, of a living 8 pound baby boy. The scar in the left tube was widely distended, but otherwise no abnormalities were noted. The patient had a normal postpartum course.

Comment

The consensus in the past has been that tubal reconstructive operations are almost always unsuccessful procedures. The picture has been further dimmed by the frequency of repeated ectopic pregnancies. Mayo and Strassmann[2] reviewed the literature and found a 3.9 per cent recurrence rate of ectopic pregnancies and advocated conservative surgery to preserve fertility. Makuda[3] studied 250 patients operated on for ectopic pregnancy and found a recurrence rate of 22.2 per cent, while 48.5 per cent remained sterile. He believed that the removal of both tubes is indicated in each case of ectopic pregnancy. On the other hand, Rubin[4] stated, "In cases of repeated ectopic pregnancy, when the patient is anxious to have a child and is willing to risk a third ectopic pregnancy, a partial salpingectomy may be performed with a plastic operation on the tube stump. The alternative of removing the gestation sac by simple incision and suture of the tube with or without curettement of the tube may be borne in mind. The feasibility and value of this procedure await further experience."

There is no doubt in the minds of most surgeons that an attempt should be made to preserve the childbearing function. Suitable criteria for such a procedure have been established by Stromme.[1] They are: "(1) early unruptured pregnancy; (2) appearance of the involved tube otherwise normal; (3) absence of, or evidence of, occlusion of the opposite tube; and (4) a strong desire by the patient and husband for more children." These conditions were present in our case.

That the operation is a valid and worth-while procedure has been proved by the 2 cases now present in the American literature and the following reports from abroad: Caffier[5] operated on 10 patients with ectopic pregnancy who had had a previous salpingectomy. Four of these patients later had intrauterine gestations. Ferry[6] in 1955 performed a tubal plastic procedure for repeated ectopic pregnancies. This was followed two years later by the delivery of a 4,800 gram living infant. Tausch[7] presented another similar case which was followed by two intrauterine pregnancies. Jauch[8] reported a case of repeated tubal pregnancy where in the second ectopic pregnancy a conservative fimbrial plastic operation was performed instead of tubal extirpation. This was followed by two intrauterine pregnancies three and four years later. Nine years after the second birth, a third ectopic pregnancy occurred, probably because of an adhesion constricting the rest of the Fallopian tube. The left adnexa were completely removed at this time.

From these reports and our own case we believe that every effort should be made to preserve the affected tube or part of it and to use the type of

plastic surgery which in each individual case gives the greatest promise of patency. This is especially important in the first ectopic pregnancy in a nulliparous woman.

Summary

A case of two successive tubal pregnancies followed by a full-term intrauterine gestation is presented, this being the second case reported in the American literature. The first ectopic pregnancy was terminated by salpingectomy, the second by salpingostomy. This ectopic pregnancy had not been diagnosed prior to operation for ovarian cyst. Its smallness allowed the complete removal through a longitudinal incision with closure in two layers without stenosis of the tubal lumen.

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FETAL GIGANTISM

An Unusually Large Newborn Infant Associated With Maternal Diabetes

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EXCESSIVELY large newborn infants are relatively uncommon. Eastman[1] designates all newborn infants weighing 4,000 grams or more as of excessive size. Koff and Potter,[2] in a study of 20,219 births at one hospital, found that 0.94 per cent of the infants weighed more than 4,500 grams. Our own incidence of infants over 4,500 grams in a series of 4,400 deliveries was 1.1 per cent. Schuyler,[3] after reviewing the literature, stated that there have been few substantiated reports of babies weighing over 6,804 grams at birth. He listed 7 cases of fetal gigantism ranging up to 11,339 grams. All the infants were delivered per vaginam. No mention was made of maternal constitutional diseases which might have accounted for these large infants. The largest baby born alive weighed 7,824 grams (17.19 pounds).[4] The head was born spontaneously, but there was difficulty delivering the shoulders. Another living newborn infant weighed 7,342 grams (16.15 pounds) and was delivered by podalic version. The remainder were stillborn.

The purpose of this paper is to add to the literature another case of fetal gigantism. This particular pregnancy was associated with maternal diabetes and some degree of postmaturity.

Case Report

G. L., a 33-year-old Negro, gravida vii, para iii, abortions iii, was admitted to the Frankford Hospital on Sept. 30, 1955, because of excessive weight gain and dependent edema. She had been followed in the prenatal clinic since June 16, 1955. When first seen, she was 5 feet 8 inches tall and weighed 270 pounds. Her last menstrual period had begun on Dec. 10, 1954, and her estimated date of confinement was calculated to be Sept. 16, 1955. Her previous menstrual history was normal. Laboratory studies done in the clinic were as follows: hemoglobin 12.1 Gm. per 100 c.c.; hematocrit 39 per cent; white blood count 5,600; blood type A, Rh positive D; Wassermann and Kline tests negative.

The patient had delivered three apparently normal male infants in 1941, 1942, and 1951, respectively. Her first baby weighed 8¾ pounds and had been delivered with forceps from an occiput posterior position after a 60 hour labor. Following delivery, she had developed a puerperal morbidity which responded well to medical therapy. She stated that she had weighed 118 pounds before this pregnancy and had gained almost 70 pounds during the pregnancy.

Labors before her second and third deliveries were described as "very long," although the exact durations are not known. These babies weighed 9 pounds and 10 pounds, 2½ ounces, respectively. She had been hospitalized five days prior to her third delivery because of slight vaginal bleeding of unexplained etiology.

The patient also gave a history of three spontaneous abortions in late 1941, 1952, and 1953, at 3, 5, and 5 months' gestation, respectively. She had had an appendectomy during childhood and a dilatation and curettage following her third abortion. Her past medical history was otherwise negative. Her family history was negative for diabetes and other significant familial diseases.

Prior to this admission, the patient had been hospitalized from Sept. 8 to 12, 1955, because of excessive weight (292 pounds), and severe edema of both legs and of the dependent portion of her protuberant abdomen. At that time she was experiencing irregular uterine contractions. Blood pressure was 136/80. Urine analysis on September 9 was negative for albumin and acetone, and 1 plus for sugar. The following day the urine sugar was reported as negative. Fasting blood sugar was 140 mg. per 100 c.c. (Folin-Wu technique), and blood urea nitrogen was 7 mg. per 100 c.c. She was treated with rest, sedation, diuretics, and a salt-free diet. Her weight decreased to 284 pounds and the edema subsided to a point where she could be discharged and followed on an outpatient basis.

On her readmission on Sept. 30, 1955, the patient was placed on a regime consisting of sedation, rest, salt-poor diet, and ammonium chloride. She weighed 276½ pounds. Blood pressures were normal. A medical induction of labor was considered. Rectal examination, however, disclosed a high vertex and a thick, uneffaced cervix.

X-ray studies of the pelvis were reported as follows: true conjugate diameter 11.9 cm., bi-ischial diameter 9.4 cm., transverse diameter of inlet 11.5 cm.; volume of pelvis 435 ml. at bi-ischial diameter; volume of fetal head 610 ml. (by Ball technique); android pelvis. The bi-ischial is low normal. No "real cephalopelvic disproportion." Single fetus with the head above the inlet. Femoral and tibial epiphyses both visible. At term.

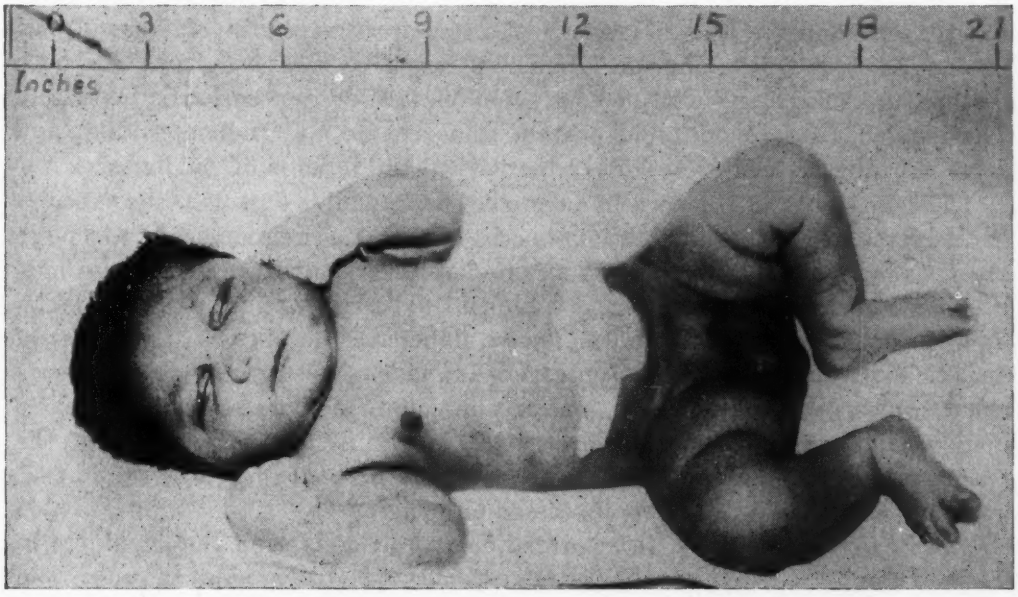

Fig 1.—The newborn during the first day of life.

A glucose tolerance test was performed on Oct. 7, 1955, and yielded the following information (Folin-Wu technique):

	BLOOD SUGAR	URINE SUGAR
Fasting	92 mg./100 c.c.	--
½ hour	170 mg./100 c.c.	Negative
1 hour	232 mg./100 c.c.	Negative
2 hour	300 mg./100 c.c.	0.25%

On Oct. 8, 1955, the day following the glucose tolerance test and three weeks past the calculated date of confinement, a low cervical cesarean section (Munro-Kerr technique) was performed. The operation and delivery were uncomplicated. A large, living, apparently normal male child was born. The infant cried immediately, was given routine cesarean section postdelivery care, and was transferred to the premature nursery for observation. His birth weight was 15 pounds, ½ ounce (6,824 grams). The baby's postnatal course was uneventful. He was circumcized on the ninth day and discharged with the mother on the following day. His weight on discharge was 13 pounds, 2½ ounces (5,972 grams), a weight loss of 1 pound, 14 ounces (852 grams) during the first ten days of life. He has remained in apparently good health.

The patient's postpartum convalescence was also good. She was kept on a diabetic diet but did not receive insulin. Daily fasting blood sugar determinations were fairly constant, ranging from 175 to 200 mg. per 100 c.c. She was discharged on the tenth postpartum day to the care of the obstetrical and diabetic clinics. Her weight on discharge was 240 pounds. At the time of her six weeks checkup, she was in apparently good health. The uterus was normal in size and the operative incision was well healed. Fasting blood sugar was 140 mg. per 100 c.c. and her diabetes was being controlled by diet without insulin.

Comment

Excessively large newborn infants pose problems from both the maternal and pediatric standpoints. Fetal size is largely dependent on the length of gestation. In Koff and Potter's[2] series of infants weighing more than 4,500 grams, the average length of gestation was 288 days. Size of parents, multiparity, advancing age, and maternal diabetes are contributing factors in producing excessive development. Labor presents a greater hazard for both mother and offspring. The necessity for operative intervention is increased. The incidence of toxemia, postpartum hemorrhage, maternal morbidity, and fetal mortality is definitely higher than when the fetus is of smaller size.

The incidence of diabetes in pregnancy is, roughly, 1 in 300 pregnancies.[5] Fetal gigantism occurs in 45 to 70 per cent of diabetic pregnancies.[9] Although great strides are being made in this direction, the very nature of diabetes mellitus is not fully understood, and it is difficult to correlate teleologically the relationship of fetal gigantism and maternal diabetes.[10, 11] Likewise, treatment of diabetic expectant mothers is a controversial and touchy subject.[12, 13, 14] We are not entirely powerless, however, for early diagnosis of diabetes can do much to increase fetal salvage. Early delivery of diabetic patients may eliminate the problems of fetal gigantism (as well as other problems) before they arise. This subject is very adequately discussed elsewhere.

In Schuyler's[3] review, there was difficulty in delivering the shoulders in 6 out of the 7 cases mentioned. In retrospect, we feel as he does that cesarean section would perhaps have salvaged all of these stillborn fetal giants. Once gigantism has occurred, vaginal delivery is fraught with unnecessary danger and cesarean section is indicated.

In the case presented here, cesarean section as the method of delivery was chosen for several reasons. First, despite the borderline x-ray measurements, the fetus seemed too large clinically for easy vaginal delivery. Second, the patient was three weeks past her estimated date of confinement, and cervical changes associated with impending labor had not occurred. Last, there

was a history of long, difficult labors associated with moderately large infants. It was therefore felt that cesarean section afforded by far the least risk to both mother and child.

Summary

A case of fetal gigantism associated with diabetes mellitus is presented. The infant, whose birth weight was 15 pounds, ½ ounce (6,824 grams), was delivered alive and well by cesarean section. The mother's postpartum course was uneventful. The literature on fetal gigantism is reviewed briefly.

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MANAGEMENT OF CONGENITAL ADRENOGENITAL SYNDROME*

A Case Report

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HERMAPHRODITISM has engaged man's fancy since antiquity. Aphrodite, the ancient Greeks' goddess of love, bore Hermes, the winged-footed messenger of the gods, a son whose body was united to that of a nymph while he played with her in a fountain. Thus the ancients explained this strange phenomenon. Even today our scientific knowledge concerning it is very meager.

Heretofore, when the gynecologist and the pediatrician were confronted with a young pseudohermaphrodite, they usually considered it necessary to perform a laparotomy to determine the true sex of the child. In the light of recent knowledge the female pseudohermaphrodite due to congenital hyperplasia of the adrenl cortex can be differentiated from the pseudohermaphrodite due to genetic aberrations. This can usually be done without laparotomy. Moreover, there now appears to be an effective treatment for this type of female pseudohermaphrodite.

We wish briefly to discuss the diagnosis, differential diagnosis, and treatment of the androgenital syndrome in the young female due to congenital adrenal hyperplasia.

A better understanding of the underlying mechanism in the development of this condition came from investigations by Bartter and his co-workers,[1] and more recently by Bongiovanni.[2, 3] It is generally agreed that a glucogenic hormone, Compound F, is biosynthesized from 17-alpha-hydroxyprogesterone and progesterone. The investigations of these workers indicate that this is normally accomplished under the catalytic influence of an enzyme which is lacking in this condition. Thus an important inhibitor of the hypophysis, namely, Compound F, is lacking. The hypophysis therefore secretes an excessive amount of ACTH in order to stimulate the adrenal glands to produce the deficient glucogenic hormone.

Although the adrenals are unable to produce Compound F, the excessive amount of ACTH stimulates them to produce substitution hormones, mainly androgenic compounds. These androgenic hormones produce the symptoms of virilization. The metabolic end products of these androgens appear in the urine as 17-ketosteroids in excessive amounts. Pregnanediol and pregnanetriol

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are produced in increased amounts, indicating that such precursors as progesterone and 17-alpha-hydroxyprogesterone may be produced in increased amounts in this condition.

In the case of the female fetus with congenital adrenal hyperplasia the masculinizing influence probably begins between the twelfth and twentieth weeks, i.e., between the sixty-third and one hundred sixty-second mm. stages,[4] interfering with the separation of the urethra and vagina, thus continuing the urogenital sinus. Most of these individuals are born with a common vaginal and urethral outlet. In a few the openings are separate. The androgenic influence also produces an enlarged clitoris which is usually evident at birth. The individual, being a female, has a uterus, tubes, and ovaries, although they are small. Aberrations of the external genitals vary.

Thus, in early childhood we have an individual who is fundamentally a female but one who is partly masculine in appearance. Growth is abnormally rapid. She is muscular. The body contour is more like that of a boy than of a girl. She has pubic hair and a clitoris as large as a penis. She has abnormally coarse hair on the face and the extremities. Below the phallus there may be two openings, but usually one representing a urogenital sinus. This opening is flanked by two folds which may suggest labia or a divided scrotum. There are no testicles. The appearance of the external genitals varies and by examination they cannot be differentiated from those of a pseudohermaphrodite of genetic origin. The use of the term genetic pseudohermaphrodite in this paper indicates one due to genetic or unknown intrauterine influences.

Differential Diagnosis

There are, however, two striking differences between the genetic pseudohermaphrodite and the female with congenital androgenic syndrome.

1. If the androgenic influence is on a genetic basis, evidences of it such as muscular hypertrophy, male contour, and hirsutism are not present before puberty, when the adrenal is activated by the pituitary gland, whereas in the congenital androgenic syndrome this influence is in evidence in infancy and early childhood.

2. If the condition is on a genetic basis, the 17-ketosteroids will remain at an infantile level and do not rise above 2 mg. per day until the onset of puberty, whereas in this condition they are high in early childhood and attain the adult female level of 8 to 14 mg. per diem or higher. The two conditions can usually be separated on these two considerations.

The next condition which must be differentiated is tumor of the adrenal cortex. In this condition there will be elevation of the 17-ketosteroids but the onset is postnatal, and, as will be discussed later, the 17-ketosteroids in congenital hyperplasia can be effectively suppressed by cortisone. In adrenal tumor they cannot.

You are familiar with the masculinizing effects of arrhenoblastoma. This is rarely a consideration in early childhood, however.

Thus, if one is confronted with a female pseudohermaphrodite with virilizing influence evident at birth and continuing through childhood with increased urinary 17-ketosteroids which can be depressed by cortisone, the presumptive diagnosis is androgenital syndrome due to adrenal cortical hyperplasia.

Treatment of the Androgenital Syndrome in the Female

Previous attempts at treatment were largely unsuccessful. Excision of part of the adrenal cortex was followed by hypertrophy of the remaining portions. Administration of estrogens resulted in breast development but had little effect on the other aspects of masculinization.[4] In 1952, Lawson Wilkins[5] published the results of his work with cortisone, which is a physiologic substitute for Compound F referred to above. He demonstrated that the administration of cortisone to the young female with the androgenital syndrome had a definite inhibiting effect on this condition. The acne disappeared, the hirsutism diminished, and breast development resulted. There was an increase in fat deposits over breasts and buttocks. Some of his patients menstruated. Wilkins[6] recommends that the patient be hospitalized and the 17-ketosteroid output be measured daily. After a base line has been established, he recommends that cortisone be administered first by intramuscular injection. By trial the lowest effective dose can be established. Then one may switch to the lowest effective oral dose which is usually two or three times as great as the intramuscular. This dose should be maintained over a long period of time with occasional checking of 17-ketosteroids in the urine.

Case Report

The treatment of the case reported here is based on this concept. The patient was treated by a team consisting of ourselves, a gynecologic surgeon, Dr. George C. Finola, a plastic surgeon, Dr. John W. Curtin, and a psychiatrist, Dr. Alfred P. Soloman.

This 9-year-old girl was referred to us by Dr. T. O. Cantwell and admitted to St. Luke's Hospital July 10, 1954, at the age of 8 because of a severe acute febrile illness with an extensive hemorrhagic rash which was diagnosed clinically and serologically as Rocky Mountain spotted fever and successfully treated with Terramycin. Sex aberrations were manifest. The case was thoroughly worked up. For brevity, only the essentials are presented here.

She is one of eight children ranging from 18 years to 3 years. Mother, father, and all children are living and well except as designated below.

An 18-year-old sister is small, 5 feet, 1 inch tall. She is muscular and masculine in contour with no breast development. She is mentally retarded and shy but fairly well adjusted. There is a history of pubic hair and enlarged clitoris since the age of 2 years. She grew rapidly, attaining a height of 5 feet at 10 years, only 1 inch less than her present height. At 14 years of age an exploratory laparotomy was performed at the Ingalls Memorial Hospital, Harvey, Illinois, and a small, underdeveloped uterus and ovaries were found. The clitoris was amputated at that time.

A brother 11 years old weighs 110 pounds and is 5 feet, 1 inch tall. The epiphyses of the hips and elbows are fused. The muscles are hypertrophied and the penis is enlarged. Pubic hair developed at the age of 18 months. He has a deep husky voice and his general appearance is that of an adolescent male. He is said to be mentally normal.

Past History.—The patient had a large clitoris at birth. Sex hair appeared early, by 2 or 3 years of age. Other masculine features developed gradually. The parents fortunately considered this child a girl and were fearful of any attempt to make her a boy.

Physical Examination on First Admission.—This 8-year-old girl was large for her age. The pelvis was of masculine configuration (Fig. 1, *A*). The thighs did not close. The face looked like a boy's when the long hair was covered. There were no breast changes. The pubic hair was marked with feminine type of distribution. The clitoris was markedly enlarged, measuring 5 cm. in length with a median raphe as in hypospadias extending into a small vaginal orifice (Fig. 2, *A*). Both labia majora were hypertrophied. The urethral meatus was situated under the clitoris near a small vaginal orifice. The hair growth on the extremities was marked. Testicles could not be palpated in the inguinal region. No neurological anomalies could be detected.

She was very morose with a completely indrawn personality. She almost never played or smiled. She would not talk to anyone in the hospital and answered questions with a grunt or nod.

Laboratory Examinations.—

X-ray examinations: Bones: There was fusion of all ossification centers of the hip, indicating a bone age of more than 16 years. Ossification of the vertebral bodies, the iliac crests, and the wrist bones indicated a bone age far beyond her chronological age.

A. *B.*

Fig. 1.—*A*, This photograph was taken July 17, 1954. Age 8 years. Notice boyish appearance of body and genitals.

B, This photograph was taken March 24, 1955, after two months of cortisone therapy. Operation was performed March 5, 1955. Note the more feminine appearance of the body and genitals.

Neurological skull films: Negative.

Vaginogram: A catheter was introduced into the urethra, another below into the small orifice of the vagina. The bladder was relatively large. On the anteroposterior projection the vagina itself was found to be normal in length and caliber.

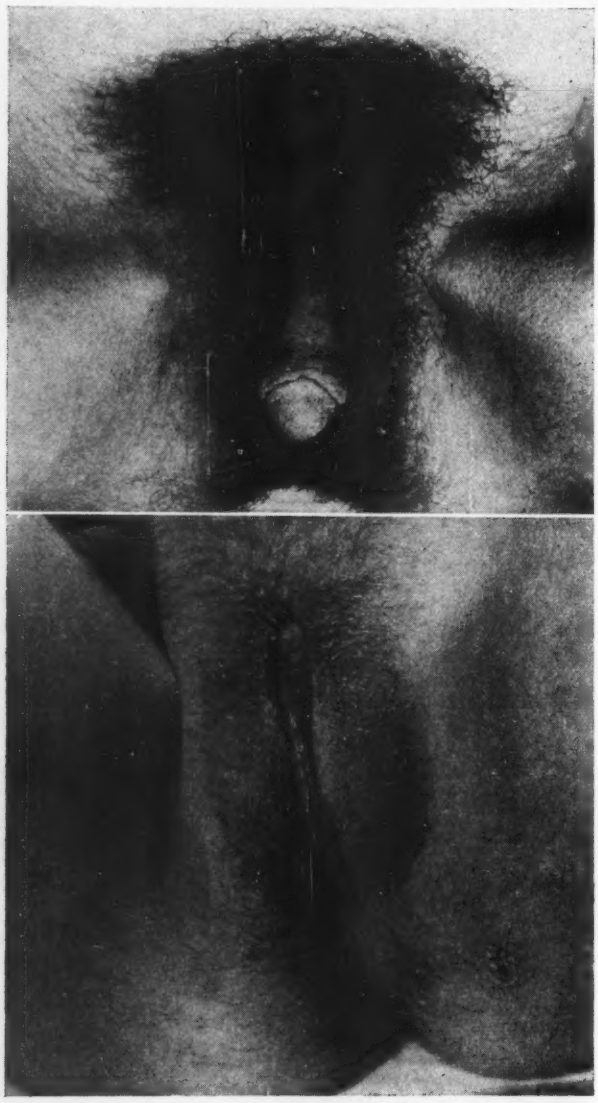
Intravenous pyelogram: Negative.

Blood chemistry: The total nonprotein nitrogen, the fasting blood sugar, the electrolytes, and the protein-bound iodine determinations were all within normal limits.

Electroencephalogram: Abnormally slow. This was taken during convalescence from Rocky Mountain spotted fever. A later electroencephalogram was regarded as bordering on abnormality without specific changes.

Exfoliative cytology: A smear taken from the vagina showed neither estrogenic nor androgenic effect, but only an atrophic type of cell usually seen during normal childhood. We are indebted to Dr. George L. Wied for this examination and report.

A.



B.

Fig. 2.—*A*, Preoperative photograph of genitals. *B*, Postoperative photograph of genitals.

Hormone bioassay: The FSH was less than 1 M.U. per 24 hours; chorionic gonadotropin negative; 17-ketosteroids 15.8 mg. per 24 hours in July, 1955, and 15.8 mg. per 24 hours in September, 1955. This September specimen was differentiated and contained 14.1 mg. 3

(alpha) hydroxy-17-ketosteroids, and 1.75 mg. 3 (beta) hydroxy-17-ketosteroids per 24 hours. Corticosteroids: 0.167 mg. per 24 hours. Estrogens were not determined, since no estrogenic activity was shown by vaginal smear. Pregnanediol and pregnanetriol were not determined.

Diagnosis.—A presumptive diagnosis of androgenital syndrome in a female child due to congenital hypertrophy of the adrenal cortex was made for the following reasons:

1. Prenatal virilization as evidenced by: (a) enlarged clitoris at birth; (b) interference with normal development of the female genitals.

2. Continuation of virilization in early childhood as evidenced by early sex hair with male skeletal characteristics and hirsutism.

3. Had these changes in the genitals demonstrated by physical examination been on a genetic basis with ovotestes, etc., there should be no evidence of hormonal activity before the age of puberty, be it virilization or feminization.

Treatment.—This girl, now 9 years of age, was readmitted to St. Luke's Hospital on Jan. 23, 1955, for treatment of the androgenital syndrome. The base line of approximately 16 mg. per day of urinary 17-ketosteroids having been established, she was given 50 mg. of cortisone daily intramuscularly for 12 days. The 17-ketosteroids dropped to between 7 and 8 mg. The dose was reduced to 25 mg. intramuscularly for 10 days. The 17-ketosteroids increased slightly, between 8 and 9 mg. We then gave a larger dose by mouth, starting at 50 mg., increasing to 87.5 over a 20 day period and were unable to get the 17-ketosteroids below 8 mg. and at one time they rose to 10 mg.

During this six-week period Dr. Solomon had been actively treating her mental state. In the early stages he regarded her as an indrawn personality bordering on schizophrenia. On his advice, operation was delayed until she was prepared for it.

Operation was performed by Dr. George C. Finola and Dr. John W. Curtin on March 5, 1955. The clitoris was amputated and a vaginal orifice constructed (Fig. 2, *B*).

The vaginal opening was now of normal size for a child of her age. Her sex as a female was confirmed by identification of a cervix. Three weeks after operation the wound had healed well. Her psychological state had definitely improved. Dr. Solomon's last note stated she was "pleasant, not afraid, and cooperated with complete trust."

She was discharged March 29, 24 days after the operation, on 75 mg. of cortisone daily by mouth, since it was believed that this amount was as effective as larger oral doses. On April 20, approximately a month later, the 17-ketosteroids were 10.2 mg.

Although the 17-ketosteroids were not suppressed as much as anticipated, the clinical condition of the child has constantly improved. Parenthetically it should be stated that ordinarily the 17-ketosteroids cannot be suppressed to normal, and in children over 8 years of age Wilkins[4] found it impossible to reduce them below 4 to 6 mg. per diem.

The body curves are more nearly feminine, hirsutism has lessened but has not disappeared. After two months of cortisone therapy the child's general appearance changed markedly, as seen in Fig. 1. There is beginning breast development. She is more responsive. This child never had acne as might have been expected.

It is too early to predict the eventual outcome in this and similar cases. We propose to keep her on cortisone for some time under observation.

Comment

In the human being true hermaphroditism is rare indeed. Pseudohermaphroditism is uncommon, yet some of these distressing situations are encountered occasionally by nearly every practicing gynecologist and pediatrician. The majority of pseudohermaphrodites are genetically female with fundamental female anatomy which has been distorted by the virilizing effects of congenital adrenal cortical hyperplasia. These individuals can with a good deal of certainty be separated from the genetic pseudohermaphrodites. This can be done by a careful history and physical examination aided

by laboratory examinations, the most important one being evaluation of the 17-ketosteroids in the urine. Other masculinizing tumors should be ruled out by appropriate measures. Then one can proceed with confidence without resorting to an exploratory laparotomy in the cases due to congenital adrenal cortical hyperplasia. It now appears that by the use of cortisone combined with good psychiatric care and good plastic surgery we have promise of converting these miserable creatures into happier and more nearly normal individuals.

Summary

We have outlined the diagnosis and differential diagnosis of female pseudohermaphroditism based on congenital adrenal hyperplasia. We have presented a family of eight children, three of whom have definite evidence of the androgenital syndrome from congenital hyperplasia of the adrenal cortex. The treatment of a 9-year-old child with this condition has been outlined following Wilkins' scheme of cortisone therapy, with emphasis on the advantage of a therapeutic team including surgeons and a psychiatrist.

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BRENNER TUMOR OF THE OVARY: A CASE OF UNUSUALLY LARGE SIZE

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IN 1907, Brenner described an ovarian tumor which he labeled "oophoroma folliculare." Since then, investigators have identified many such neoplasms. By 1946, 319 cases were reported.[1] Kerpe and associates[1] have recently rediscovered a report by MacNaughton-Jones (1898) which they regard as the first authentic description of this neoplasm.

The most widely accepted theory is that Brenner tumors originate from "Walthard rests."[2] This hypothesis has been subdivided into two separate theories, depending upon whether one considers these nests of cells embryonic (in the Cohnheim sense) or derived from the surface epithelium of the adult ovary.[3] This latter theory was proposed by Robert Meyer, who sharply defined the pathological characteristics of the tumor as we know them today.[2, 4] From histological studies of his own and from specific evidence of others, Greene[3] concludes that Brenner tumors probably have several different modes of origin, i.e., from the ovarian surface epithelium, from the rete ovarii, and from the ovarian stroma.

Teoh,[5] in a recent report, stated that both Brenner and granulosa-cell tumors have the same histogenesis and the same capacity for divergent differentiation to form epithelial and thecal cells. He believed that they arise, not from Walthard nests, but rather from ovarian follicular tissue (as Brenner originally suggested) and that a sharp separation of granulosa-theca-cell and Brenner tumors on the basis of endocrine activity is not a valid one. The histogenesis of Brenner tumors is thus a moot point at present.

Briefly, Brenner tumors have the following characteristics: Their incidence is rare. They occur most frequently in women beyond the menopause. They have no endocrine effect. They have been considered benign, but lately several malignant Brenner tumors have been reported.[6, 7] They are usually slow growing and small, and only rarely do they reach sufficient size to produce symptoms. They are usually unilateral (90 per cent). Occasionally they occur concomitantly with other ovarian tumors.[8] Grossly the tumor resembles a fibroma. No definite capsule is present, but the ovarian stroma is more or less compressed. Microscopically, two constituents are present: the characteristic nests of epithelial cells and the fibromatous connective tissue groundwork surrounding the epithelial islands.[2] Although the line of division is not

†Dr. David Promin died suddenly on May 26, 1956.

sharp, Brenner tumors may be classified as "solid" or "cystic," depending upon whether the preponderance is of Brenner epithelium or of pseudomucinous epithelium, respectively.[4]

Recently, Reel[10] described a solid Brenner tumor that weighed 12¾ pounds (5.8 kg.). The largest solid Brenner tumor recorded is one described by Neimann[9] that weighed 15 pounds (6.9 kg.). The purpose of this paper is to report a case of solid Brenner tumor weighing 19.16 pounds (8.7 kg.).

Case Report

A. M., a 70-year-old white woman, was admitted to the Frankford Hospital on Aug. 18, 1955, because of an obvious abdominal tumor. She could not recall exactly when abdominal enlargement first became noticeable. Her only symptoms were a feeling of weight in the abdomen, shortness of breath, and ankle swelling. The patient had been under the care of her family doctor for dependent edema and had received diuretics.

Her past medical history contained no relevant points, nor did her family history.

The patient's menses had begun at the age of 14, occurring regularly every 30 days with a moderate flow lasting 4 days. These periods had been associated with severe dysmenorrhea. She had been married since the age of 35, was never able to conceive, but never sought medical advice concerning her infertility. The menopause occurred at the age of 50 without any disturbing symptoms. She had had no episodes of postmenopausal bleeding.

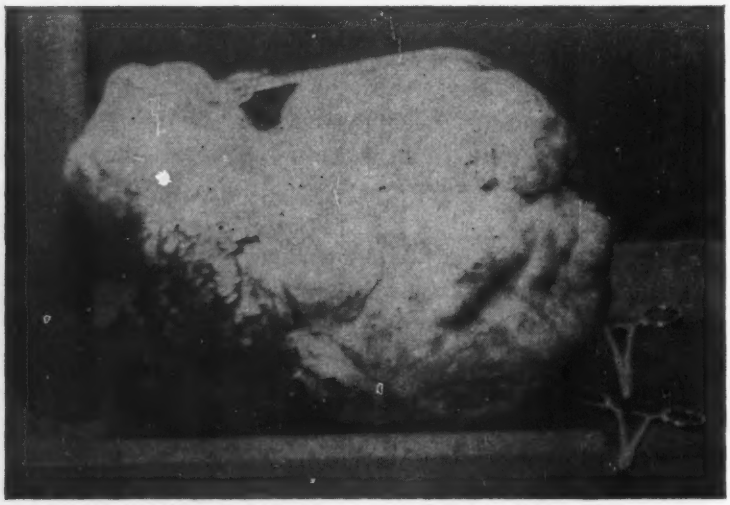

Fig. 1.—Gross appearance of the Brenner tumor.

Upon examination, the patient's general condition was found to be good. The hair distribution was, however, of interest. There was excessive hair in the beard and moustache areas for which the patient used a depilatory cream twice weekly. Her scalp hairline was of a masculine variety. Pubic and axillary hair was scanty.

A hard, irregular, ovoid mass was palpable in the abdomen. This massive tumor extended from above the costal margin down to the symphysis pubis, making examination of the other abdominal organs impossible. The mass could be moved only slightly from side to side.

Pelvic examination showed atrophic changes in the external genitals. The clitoris was normal in size. The uterus and cervix were both immovable, apparently well fixed to the abdominal mass.

The tentative diagnoses were: (1) Uterine fibromyoma? (2) Ovarian tumor? (3) Arteriosclerotic cardiovascular disease.

Clinical laboratory studies were not unusual for a person of this age. An intravenous urogram showed a tendency to blunting of the calyces of the right kidney, but no other abnormality. The radiographic features of the tumor were suggestive of a very large ovarian cyst.

An operation was performed under general anesthesia on Aug. 23, 1955. A vertical midline incision was made through the anterior abdominal wall from just below the umbilicus to the symphysis pubis. The superior end of the incision was extended obliquely to the left for a distance of 6 inches. The peritoneal cavity was entered and a large, white, hard, irregularly lobed mass was seen. There were no adhesions and the mass was easily mobilized. It was then lifted slowly and cautiously out of the abdominal incision. Several heavy clamps were immediately placed across the pedicle, the pedicle was cut, and the tumor removed. The neoplasm appeared to have been attached to the uterus at the left cornu. The left ovary and oviduct were apparently removed with the tumor. A total hysterectomy and a right salpingo-oophorectomy were then performed. The patient's postoperative convalescence was uneventful. She was discharged on the fifteenth postoperative day.

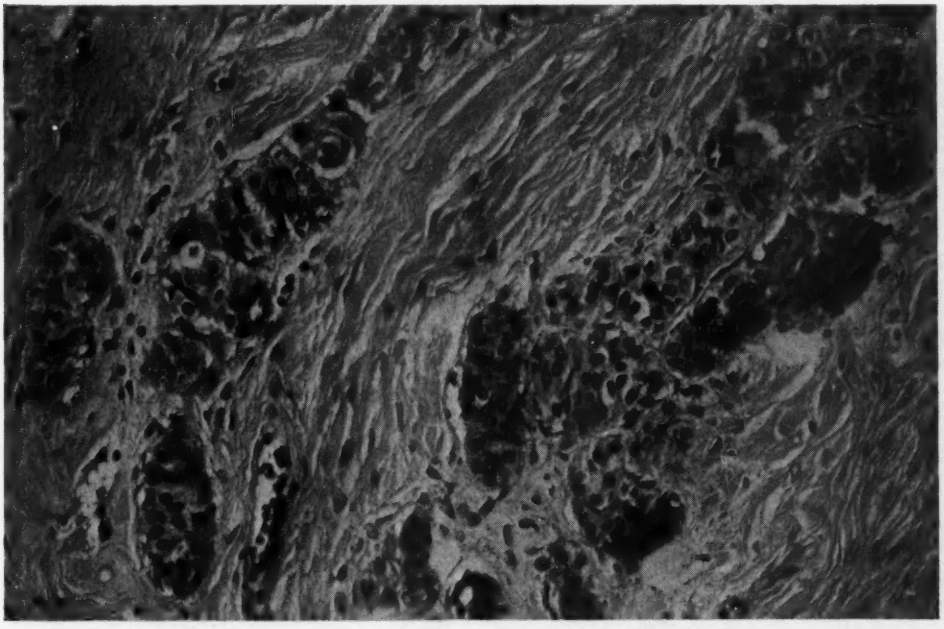

Fig. 2.—Microscopic appearance of the Brenner tumor showing the fibrous stroma and the typical nests of Brenner cells.

The pathologist's report was as follows: The specimen was a large tumor mass weighing 8,700 Gm. (19.17 pounds), multinodular and grayish pink in color, and hard in consistency. On section, the tumor mass was remarkably firm and presented areas of cystic degeneration containing yellowish fluid. To the mass was attached a Fallopian tube showing no gross pathology other than stretching apparently produced by the tumor growth. Sections of the tumor showed it to consist of a background of dense fibrocollagenous tissue in which there were cords and nests of cells. The majority of these cords of cells were solid cell masses. Many, however, showed slight cystic dilatation with their central portions containing a pink-staining material.

Microscopic sections of the tumor were forwarded to Dr. Emil Novak, Chairman of the Ovarian Tumor Registry, who confirmed the diagnosis of Brenner tumor.

Summary

A case of an unusually large solid Brenner tumor of the ovary is reported. The tumor weighed 8.7 kg. (19.16 pounds). The histogenesis and the clinical and pathological features of Brenner tumors are reviewed briefly.

We are indebted to Dr. Lester Rauer, Director of Pathology, for his interest in this paper.

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HERPES PROGENITALIS IN A WOMAN

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GENITAL herpetic infection in females has received relatively little attention. Sharlit[1] quoted Unna (1882) as having seen many cases in prostitutes and stressed the venereal spread of the disease. Charlit also commented on the relatively low prevalence in females in comparison with the amount of herpes progenitalis seen in males. Slavin and Gavett[2] described three cases of vulvovaginitis all of which yielded herpes simplex virus by inoculation of experimental animals with material from the local lesions; all three persons developed a rise in titer of neutralizing antibodies. These authors concluded that primary herpetic vulvovaginitis may be a clinically distinct disease. Lazar[3] reported two cases of primary vulvovaginitis in adults and one in a child. Krugman[4] cited a case in a child. Herpes virus was recovered from each patient and all persons developed neutralizing antibodies. Localized recurrences of lesions at the time of menstrual periods are prone to occur.[2, 3] The case described in this report illustrates the fact that a definite diagnosis may be difficult or impossible early in the illness.

Case Report

A 19-year-old single Mongolian student, three weeks after first intercourse, developed a purulent vaginal discharge associated with dysuria, nausea and intermittent right lower quadrant soreness. Her last menstrual period was 17 days before. These symptoms continued but were unknown to the physician who gave her injections (routine in connection with school) of tetanus toxoid (0.5 ml.), typhoid-para A-para B vaccine (0.5 ml.), and vaccinia on the third day of illness.

When she was seen on the fourth day of illness her oral temperature was 101° F. and pulse rate 120. The sites of injection were red, indurated, and slightly tender. There was slight tenderness to pressure over both lower quadrants of the abdomen. The cervical and vaginal mucosa were diffusely red and there was a profuse, thick, seropurulent cervical discharge. A smear of this exudate showed many polymorphonuclear leukocytes, a relatively large number of mononuclear cells, and few epithelial cells; no multinucleate cells or cells with inclusion bodies were seen. Few gram-positive cocci and many gram-negative bacilli were observed. Culture yielded beta hemolytic streptococci and *Micrococcus aureus* (Staphylococcus). The white blood cell count was 10,200 with 76 per cent polymorphonuclear leukocytes. Microscopic examination of sediment from catheterized urine showed a few cocci and 20 white blood cells per high-power field. Culture of the urine yielded Staphylococci. The blood Wassermann reaction and the heterophil sheep cell test were negative.

The patient remained febrile, with a temperature of 100 to 102.8° F. for the next four days; on the sixth day of illness the vaginal mucosa had patchy areas of redness

covered with whitish purulent material. There was a purulent discharge from the urethra and the labia were markedly edematous and red. She was unable to void and was catheterized. On the seventh day of illness the cervix was covered by a whitish membrane which extended to include parts of the vagina. Small ulcerated areas were seen on the cervix and on the vulva. The labia were also covered by a similar yellowish-white membrane. There were several erythematous, ulcerated lesions on the adjacent areas of the thighs. Smears from these ulcerated areas showed a cellular exudate similar to that previously described, except that the only bacteria seen were a few scattered gram-positive cocci. Swabs of exudate were eluted in broth containing penicillin and streptomycin and inoculated intracerebrally in mice. Herpes simplex virus was isolated. The vaginal and cervical lesions cleared during the next week and new lesions appeared on the labia and thighs. She became asymptomatic by the thirtieth day after the onset of illness, except for a slight yellowish cervical discharge. No trichomonads or Candida were found in this exudate. Following recovery the patient had a few vesicular labial lesions which appeared during three of the next five menstrual periods. Before the present episode she never had had any known skin lesions which might have been herpetic in origin. The virus obtained produced a fatal encephalitis in mice by intracerebral injection. Pocks were produced on the chorioallantoic membrane of embryonated eggs. Inoculation of the cornea of rabbits resulted in a keratitis with epithelial intranuclear inclusions. The virus isolated in mice was tested for neutralization with the patient's sera obtained on the twenty-eighth and fifty-third days after the onset of illness and with known herpes immune rabbit serum (MacIntyre strain) sent by Dr. E. H. Lennette, California State Department of Public Health. The neutralization tests were done by addition of 5 MLD_{50} of infected mouse brain (diluted in tryptose phosphate broth) to equal volumes of serial twofold dilutions of serum. Seven mice each received intracerebrally 0.03 ml. of each mixture. Control mice were given virus mixed with normal rabbit serum. Mice were protected by both samples of the patient's serum in a dilution of 1:32 and by the immune rabbit serum diluted 1:8.

In addition to supportive treatment the patient received penicillin, Achromycin, and triple sulfonamides before the nonbacterial nature of the infection was realized. Sitz baths provided considerable symptomatic relief.

Comment

From the preceding protocol it is apparent that a definite diagnosis was difficult during the first week of illness. The possibility of acute gonorrhea was not supported by direct smear or culture nor by the finding of numerous mononuclear cells in the exudate. The lesions apparently initially involved the cervix and adjacent vagina and later appeared on the vulva and thighs. The appearance of the external lesions was unlike the milder vulvar lesions frequently associated with Candida or Trichomonas infection; this suggested the possibility of herpetic infection. The serum of the patient obtained on the twenty-eighth day of illness contained neutralizing antibodies. These may have been present in response to a previous herpetic infection. It is more likely that they resulted from the present illness which was a primary infection with herpes simplex virus.

Present evidence suggests that most individuals acquire subclinical herpetic infection relatively early in life.[5, 6] The rare, initial clinically apparent disease is characterized by lesions of the oral mucous membranes or skin and uncommonly the genitals. Consequently, relatively few adults have escaped infection and one might expect that few of these individuals would acquire

their infection by chance venereal contact with an individual who had genital herpetic lesions. Once acquired, however, the genital infection might be expected to recur in an unknown percentage of individuals. Whether the majority of recurrent genital herpetic infections are of venereal origin is a matter of speculation. Possibly many are accidentally transferred mechanically from recurrent herpetic lesions elsewhere on the person's own body; if this occurs it is unlikely that a severe genital infection would result unless it happened during the course of a primary infection.

The present report illustrates the difficulty in early diagnosis of genital herpes that may be encountered in females before discrete lesions appear. The failure to demonstrate a microbial origin and the lack of response to antibiotics led to suspicion of a virus as the cause for the illness. The virus of herpes simplex is not susceptible to any known drug and the infection is self-limited. Continued use of antibiotics during the course of the disease would be expensive and potentially dangerous because of toxic reactions. Supportive treatment is indicated. Such treatment would not be used for other venereal diseases for which specific chemotherapy is available. Herpetic infection differs from candidiasis or trichomoniasis in both treatment and prognosis.

Summary

A case of genital herpes simplex infection in a female is presented and discussed.

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PROLAPSE OF A FALLOPIAN TUBE AS A COMPLICATION OF HYSTERECTOMY

Report of Three Cases

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PROLAPSE of a Fallopian tube through the vaginal vault is an unusual complication following hysterectomy. That this can occur does not appear to be commonly known. In our experience the prolapsed portion of the oviduct has not been recognized as such for prolonged periods despite frequent vaginal examinations. We have encountered three instances of this interesting complication which we wish to report.

CASE 1.—A 50-year-old woman, para ii, first registered at the Clinic in September, 1948. She complained of lower abdominal pain and a sensation of pelvic pressure. Subtotal hysterectomy, performed elsewhere, had failed to relieve her of these symptoms. Positive physical findings, limited to the pelvis, consisted of a grade 2 rectocele and grade 2 descensus of a large, cystic, cervical stump. The cervical stump and remnant of the uterus were removed by what amounted to a technique for vaginal hysterectomy, and perineorrhaphy was performed. The patient was dismissed from our care on the fourteenth day after an uncomplicated postoperative course. The vaginal vault appeared to be healing satisfactorily at that time.

The patient when next seen, in November, 1949, complained of an offensive vaginal discharge and dyspareunia. She had noted the onset of these symptoms soon after operation. Although her family physician had repeatedly cauterized what appeared to be vaginal granulation tissue, the symptoms had persisted. Pelvic examination showed a vagina of normal depth and diameter with good support. In the center of the vaginal vault there was a defect 1 cm. in diameter through which projected a polyp, also 1 cm. in diameter, that looked like granulation tissue. This site seemed to be the source of the patient's discharge and pain. Biopsy of the pedunculated tissue in the vaginal vault, performed with the patient under thiopental (Pentothal) sodium anesthesia, disclosed it to be a Fallopian tube. After an elliptical incision had been made around the area, most of the right Fallopian tube could be delivered by traction; then the base was ligated, the tube was excised and the vaginal vault was reconstructed. The patient was completely relieved of her gynecologic symptoms.

CASE 2.—A 28-year-old woman, para iii, gave a history of intractable menorrhagia for which vaginal hysterectomy had been done in November, 1952. Two weeks after the operation the patient again was hospitalized with symptoms consisting of high fever, dysuria, lower abdominal pain, and a malodorous, bloody, vaginal discharge. Several

*The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

similar attacks requiring hospitalization occurred thereafter. Despite periodic cauterization of granulation tissue in the vaginal vault and administration of antibiotics, a profuse vaginal discharge, some bleeding of a cyclic nature, and severe dyspareunia had been present for 2½ years when the patient first consulted us in April, 1955. A general physical examination revealed only slight suprapubic tenderness. In the left corner of the vaginal vault there was a red, polypoid cluster of tissue that measured 2 cm. in diameter and projected through a defect in the vaginal mucosa. The mass was relatively tenacious and unyielding but attempts to remove it produced severe pain, a phenomenon that is not characteristic of granulation tissue. A probe inserted just medial to the prolapsed tissue seemed to enter the abdominal cavity without encountering any resistance. A tentative diagnosis of prolapsed oviduct was confirmed by biopsy.

After the patient was anesthetized with thiopental sodium, the vaginal vault was opened and the ampullary portion of the left Fallopian tube was found to be prolapsed. Bilateral salpingectomy was performed. The gynecologic symptoms were completely relieved and the acute febrile attacks had not recurred when the patient was last seen.

CASE 3.—A 51-year-old woman, para iv, had been examined at the Clinic on several occasions and found to have small uterine fibroids. An emergency total abdominal hysterectomy was performed elsewhere in September, 1955, for menorrhagia with secondary anemia. The postoperative course was said to have been uneventful until the seventh day when severe lower abdominal pain developed and considerable bright-red blood was passed by vagina. The bleeding subsided spontaneously but then recurred on the fourteenth postoperative day. A moderate amount of offensive vaginal discharge had been noted daily during the approximately 6-month interval between hysterectomy and registration at the Clinic in February, 1956. The positive physical findings were limited to the pelvis. In the midline of the vaginal vault a tag of bright-red tissue 1.5 cm. in diameter was visible. This was assumed to be granulation tissue and was removed with biopsy forceps, resulting in considerable discomfort for the patient. An unusual amount of bleeding followed, which required use of an absorbable gelatin sponge (Gelfoam) and an iodoform-gauze pack for its control. The biopsy specimen showed a picture consistent with that of salpingitis. With the patient under thiopental sodium anesthesia, incision was made around the defect in the vaginal vault and an inflammatory mass was found, consisting of the prolapsed left Fallopian tube which was surrounded by considerable inflammatory reaction. The ampullary portion of the right tube also was adherent at the same site and was removed. No complications occurred during the postoperative period. The vaginal discharge previously noted had disappeared when the patient was last seen.

Comment

Although Kennedy and Campbell[1] implied that prolapse of the Fallopian tube is a relatively common postoperative complication, McElin and Ferris[2] could find but 6 documented cases [3-7] in the literature prior to 1949, when they reported 2 cases. To these may be added our 3 cases and 9 others reported since 1949,[8-11] making a total of 20 cases.

The idea that the tube can prolapse only after vaginal hysterectomy has been dispelled by Funnell and Kelso,[12] who reported that the prolapse in 2 of their cases followed abdominal hysterectomy, as it did in our third case (Table I). The complication also has been noted following colpotomy[3] and an interposition operation.[4] It was the experience of Kennedy and Campbell[1] that the left tube was always involved; however, in 3 instances, including our first case, the right tube has been the one to prolapse. As a rule, the fimbriated end of the oviduct has projected completely through the vaginal vault. Less commonly, this portion of the tube has become occluded above the vaginal vault during closure of the peritoneum. In one instance in our experience, this resulted in formation of a large hydrosalpinx that led to abdominal exploration for suspected ovarian disease.

In 15 of the 20 reported cases single or multiple factors could have predisposed to the prolapse (Table II). It appears that prolapse of the oviduct may take place in patients who have had prolonged postoperative morbidity, or postoperative bleeding, or both, hematomas, vaginitis, or abscess formation. The use of gauze packs and drains in the cul-de-sac and the clamp method of vaginal hysterectomy are mentioned in several reports. These would provide obvious peritoneal defects through which the extremity of the tube could prolapse; fortunately, both techniques have been largely abandoned.

TABLE I. PROLAPSE OF FALLOPIAN TUBE: DISTRIBUTION OF CASES ACCORDING TO TYPE OF OPERATION THAT PRECEDED PROLAPSE

OPERATION		CASES
Vaginal hysterectomy		15
Mayo type	2	
Heaney type	3	
Clamp method	1	
Method not stated	9	
Abdominal hysterectomy		3
Interposition operation		1
Colpotomy; abdominal right salpingo-oophorectomy		1
Total		20

TABLE II. PROLAPSE OF FALLOPIAN TUBE: DISTRIBUTION OF CASES ACCORDING TO PREDISPOSING CONDITION (15 CASES)

PREDISPOSING CONDITION	CASES
Febrile postoperative course	11
Postoperative bleeding or hematoma	8
Emergency or difficult operation	4
Poor condition of patient	2
Vaginitis; abscess	3
Pack or drain in cul-de-sac	3

Failure to obtain separate and accurate closure of the peritoneum, snug fixation of the stumps of the ligaments, or good hemostasis in particular would predispose to development of this complication. Funnell and Kelso[12] got the impression that, in addition to poor surgical technique, infection or hematoma formation must be present to cause separation of the suture line. In this respect, the reports of Pratt and Scherman[9] and others demonstrating the value of preoperative cleansing of the vagina with soap and water and the use of penicillin suppositories in reducing posthysterectomy infection and morbidity seem to be pertinent. Postoperative bleeding and hematoma formation remain the major complications following vaginal hysterectomy; perhaps this explains the higher incidence of prolapsed oviduct following vaginal rather than abdominal hysterectomy.

Diagnosis.—The onset of symptoms related to the prolapse may be noted immediately or may be delayed as much as 1 year (Table III). In most instances symptoms have appeared in less than 3 months after hysterectomy. Three of the 20 patients reported on were asymptomatic. A profuse, watery, malodorous, and frequently blood tinged discharge, lower abdominal pain perhaps localized to the side of tubal prolapse, and dyspareunia are the prevalent symptoms. The condition should be suspected in any patient who has a persistent vaginal discharge following a complicated posthysterectomy convalescence. The most common clinical diagnosis has been vaginal granulation tissue. As a rule, this diagnosis can be readily excluded since this tissue is much more friable and its removal is less painful than is true of tubal tissue.

Insertion of a small probe into the lumen of the tube or into the abdominal cavity, as in our second case, can be considered a specific aid in establishing the diagnosis. Obviously, before treatment is instituted biopsy should be performed in all cases to exclude other lesions that may appear in the vaginal vault, namely, benign papilloma, condyloma acuminatum, granuloma, prolapsed omentum, ovary, or loop of bowel, endometriosis, and recurrent malignant lesion.

TABLE III. PROLAPSE OF FALLOPIAN TUBE: DISTRIBUTION OF CASES ACCORDING TO TIME OF ONSET AND NATURE OF SYMPTOMS

ONSET, INTERVAL AFTER OPERATION	CASES			
	TOTAL	DISCHARGE	BLEEDING	PAIN
0 to 7 days	4	4	3	4
2 to several weeks*	6	6	3	4
1 to 2 months	4	3	3	1
3 to 4 months	2	2	1	
1 year	1	1	1	1
No symptoms	3			
Totals	20	16	11	10

*Includes statement "soon after dismissal from hospital."

Treatment.—The management of the prolapsed portion of the tube has varied from simple cauterization in the office to abdominal salpingectomy. In 2 of our cases and in several of those reported, the prolapse persisted and symptoms continued despite repeated cauterization. It appears that the proper treatment should consist of general anesthesia and the making of an elliptical incision around the tube followed by traction and high ligation or total salpingectomy and by complete closure of the vaginal vault. Abdominal salpingectomy rarely seems indicated, although Ferraris[10] has suggested that this is the procedure of choice.

Summary

We have reported 3 instances of prolapse of a Fallopian tube through the vaginal vault as an unusual, infrequently recognized complication of hysterectomy. The pertinent clinical features of these and the 17 cases previously reported in the literature have been tabulated.

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Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

The Clinical Management of Varicose Veins. By D. W. Barrow. Second edition, 169 pages with 70 illustrations. New York, 1957, Paul B. Hoeber, Inc. $6.00.

Concerning the management of varicose veins, there is a continuous flow of new books, new editions of old books, and numerous articles in the medical press. The second edition of a successful book should help to meet the demand for modern information about a common disabling condition. Although it is a small book, the subject is comprehensively covered. The text is arranged in an orderly fashion and the opening chapters on anatomy, physiology, and pathology are clearly written and adequately illustrated.

In our opinion, more emphasis could have been given to the value of injection treatment in pregnancy. We must disagree with the statement concerning the vulva "that veins thrombosed by sclerosing solutions in this region tend to remain painful and tender for protracted periods." Furthermore, the statement that "quinine urethane injections are not advised during pregnancy or menstruation" is misleading. The amount of quinine used is so small that the parturient uterus would not be activated or the menstruating uterus become painful. Nowadays, however, few people use quinine urethane or sodium morrhuate. Pregnancy is stated not to be a contraindication to operative treatment. We agree, but find that injection treatment is better and has the further advantage that hospitalization is not required.

The chapters on the treatment of varicose veins of the long and short saphenous system are really excellent. Proper emphasis is given to failure of operative treatment by neglecting to test and treat the competence of the veins communicating between the deep and superficial venous systems. The short concluding chapters on complications, thrombophlebitis, and aftercare of the varicose extremities are sufficiently informative. Altogether, this is a book that can be recommended.

Esterilidad Conjugal. Edited by N. Arenas, A. E. Bettinotti, and E. G. Murray. 409 pages, 106 illustrations. Buenos Aires, 1956, Editorial Bibliografica Argentina.

Written in Spanish with contributions by 17 collaborators, this book is an encyclopedia on the subject of human infertility. Most of the statistics included are derived from the sterility service of the Ramos Majia Hospital in Buenos Aires.

In the introductory chapter Dr. Arenas states that a couple should be considered infertile if no conception has occurred after three years of involuntary sterility. Six months to a year is usually sufficient time to wait before investigation. Chapters on the physiology

and physiopathology of female infertility are included in the book. Dr. Persico describes a noninflammatory cervical discharge presumably present in women who have ovarian deficiency and/or hypoplasia. The reviewer has found no good evidence to support the existence of such an entity. In Chapter 7 Dr. Murray discusses the basal body temperature and vaginal smear. The fall in temperature is used to predict a threatened abortion. The observation has not been confirmed by others. The chapters on vaginal cytology, crystallization of the cervical mucus, and endometrial biopsy are good, but the photographs of endometria are poor reproductions.

Hysterosalpingography is performed with an oil radiopaque substance and no manometric control. The photographs of roentgenograms reported to be typical of endocervicitis, uterine hypoplasia, genital tuberculosis, and bicornuate uterus are not specific. The chapter on peritoneal adhesions by Dr. Murray includes some of his recommendations for removing these adhesions, such as estrogen, physiotherapy, vitamin A, insufflation with ACTH, and hydrotubation with antibiotics and hyaluronidase. The chapter on nutrition and vitamins in infertility by Dr. Costa implicates the vitamins as causative factors in infertility. The scientific basis for his statements at times seem to be tenuous. The book also includes chapters on semen analysis, testicular histopathology, physiology of the male genitals, and diagnosis and treatment of male sterility. An interesting note is presented on kymographic insufflation of the vas deferens to demonstrate patency. Several chapters are devoted to the medical and surgical treatment of the infertile female, endocrinology, and endocrine therapy.

The paper and printing of the book are excellent. There are English summaries at the end of each chapter. The illustrations are generally good.

Histologischer Atlas gynäkologischer Erkrangungen. By Herbert Lax. 199 pages, 199 illustrations. Leipzig, 1956, Veb Georg Verlag. 92 DM.

The purpose of this book is to aid physicians in selecting appropriate therapy by pointing out the structural changes which occur in various gynecologic diseases. Original microscopic views have been copied in color by an artist in such a way that basic anatomic changes are as obvious as one might see under the low-power objective of a microscope. The fine cellular detail will not be found here that would be expected in an atlas of photomicrographs, so that, in a sense, the title is somewhat misleading. As a companion to the pictures, the author has written a clear and concise text to explain pathologic physiology and philosophy underlying various changes. This book would be of value even to those whose knowledge of German is limited to understanding the titles of the pictures.

Surgery for General Practice. By Victor Richards. 947 pages, 476 illustrations. St. Louis, 1956, The C. V. Mosby Co. $17.50.

Dr. Richards and his collaborators from Stanford have brought together in this volume a considerable amount of well-organized, easily read material. Their objective, to provide an outline of problems encountered in all surgical fields, together with an outline of accepted modes of therapy, has obviously been reached.

The chapters dealing with local and regional anesthesia are more complete and detailed than the remainder of the book, and are particularly well illustrated. All of the material relating to the peripheral nerves is exceptionally good and is presented in considerable detail; this material too is more extensively illustrated than most of the other subject matter. The sections on urology and those on the ear, nose, and throat are considerably longer than others and seem to this reviewer to be particularly well suited as reference monographs for teaching medical students. For some reason, the chapter entitled "Infections of the Central Nervous System" deals more with various congenital lesions of the central nervous system and skull than it does with infections; this is probably a typographical error.

The concluding principle of Chapter Three is particularly important. Unqualified doctors should not, as they often do, proceed blindly with ill-chosen repairs in their haste to close wounds and to repair bones, tendons, nerves, and vessels. Instead, they should clean wounds and apply proper first-aid therapy preparatory to referral of patients to well-qualified surgeons.

Although many of the chapters seem unduly short, the majority are extremely well outlined and cover the basic material satisfactorily. The entire volume is abundantly illustrated, particularly with many original line and shaded drawings of excellent quality.

BOOKS RECEIVED

The following books have been received. Selected reviews will appear in later issues.

Actualités gynécologiques. By P. Funk-Brentano. Second edition, 1686 pages, 73 figures. Paris, 1957, L'Expansion scientifique française. 5,000 francs.

The American Fluoridation Experiment. By F. B. Exner and G. L. Waldbott. 277 pages. New York City, 1957, The Devin-Adair Co. $3.75.

Atlas of Clinical Endocrinology. By H. Lisser and R. F. Escamilla. 476 pages, 139 plates. St. Louis, 1957, The C. V. Mosby Co. $18.75.

Expectant Motherhood. By N. J. Eastman. Third edition, 198 pages. Boston, 1957, Little, Brown & Co. $1.75.

Gynecologic Therapy. By W. Bickers. 158 pages. Springfield, Ill., 1957, Charles C Thomas, $4.25.

Mesenchymal Disease in Childhood. Pediatric Research Conference. 104 pages. Columbus, Ohio, 1957, Ross Laboratories.

Les Méthodes psychosomatiques d'Accouchement sans Douleur. By D. L. Chertok. 268 pages. Paris, 1957, L'Expansion scientifique française.

Modern Therapy in Neurology. By F. M. Forster. 792 pages. St. Louis, 1957, The C. V. Mosby Co. $12.00.

Munro Kerr's Operative Obstetrics. By J. C. Moir. Sixth edition, 1008 pages, 403 figures. Baltimore, 1957, Williams & Wilkins Co. $20.

Principles of Urology. By M. F. Campbell. 622 pages, 319 illustrations. Philadelphia, 1957, W. B. Saunders Co. $9.50.

The Sanctity of Life. By G. Williams. 350 pages. New York City, 1957, Alfred A. Knopf, Inc. $5.00.

Therapeutic Exercise. By M. Williams and C. Worthingham. 127 pages. Philadelphia, 1957, W. B. Saunders Co. $3.50.

SELECTED ABSTRACTS*

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*Danielsson, C. O., Franksson, C., and Petersen, I.: Stress Incontinence Following the Manchester Operation for Prolapse, p. 337.

*Lange, P.: Value and Risk of Pertubal Insufflation, p. 354.

*Zettergren, L.: The Histogenesis of Uterine Myomata, p. 366.

*Zachariae, F.: Vaginitis Emphysematosa, p. 393.

*Trolle, D.: The Clinical Usefulness of Vulvar Fluorescence for Estimation of Estrogenic Activity, p. 404.

*Borglin, N. E.: On the Metabolism of Choline in Pregnancy, p. 424.

*Dyggve, H. V., Dam, H., and Søndergaard, E.: Influence on the Prothrombin Time of Breast-Fed Newborn Babies of One Single Dose of Vitamin K, or Synkayvite, Given to the Mother Within Two Hours After Birth, p. 440.

*Fredrikson, H., and Anberg, A.: Delivery of Elderly Primigravidas, p. 483.

*Kjessler, A.: The Time Factor in Rupture of the Membranes and Its Influence on Perinatal Fetal Mortality, p. 495.

*Jedberg, H.: Female Genital Tuberculosis and Pregnancy, p. 535.

*Brosset, A.: Maternal Morbidity and Fetal Mortality Associated With Breech Delivery, p. 546.

*Dahlberg, B.: Adenocarcinoma in One Horn of Uterus Duplex, p. 563.

Danielsson, Franksson, and Petersen: Stress Incontinence Following the Manchester Operation for Prolapse, p. 337.

The symptoms attending prolapse of the vagina and uterus usually include disturbances of micturition which ordinarily subside after operative treatment of the prolapse. In some cases, however, these disturbances persist or are aggravated. Similar disturbances may even develop postoperatively. In the present investigation the authors sought to elucidate the causes of stress incontinence following operations for prolapse in 12 women between the ages of 35 and 75 years. The operative technique was largely that reported by the Manchester school. The patients were investigated with urography, urethrocystography, urethrocystoscopy, cystometry, urinary sediment analysis, vaginal examination, and electromyographic examination of striated urethral sphincter and pubococcygeus muscles. At electromyography, electrodes were inserted into the respective muscles, and the action potentials were recorded with a cathode ray oscillograph. In none of the patients did electromyographic examination of the striated urethral sphincter disclose any electrical activity in its dorsal part nearest the vagina, at approximately 5 to 7 o'clock. This is a regular finding in women who have borne children and points to a defect in the sphincter muscle. In operations on such patients who were incontinent, the muscle was observed to be replaced by scar tissue in this dorsal part of the sphincter. In 9 cases the electromyograms were suggestive of similar defects in other parts of the sphincter as well. All, save one patient, showed normal electromyograms from the levators. It seemed evident to the authors that both cicatrization in the muscles and nerve lesions may follow parturition as well as operations for prolapse. The electromyographic examination made it

*Titles preceded by an asterisk are abstracted below.

possible to localize the defects in the sphincter. Considerable therapeutic significance was attached to this fact, since the injured part of the sphincter can be identified, resected, and repaired. In some cases it may be possible to repair the sphincter at the operation for prolapse, since defects of the striated urethral sphincter are presumably responsible for the incontinence.

ROBERT E. L. NESBITT, JR.

Lange: Value and Risk of Pertubal Insufflation, p. 354.

Uterotubal insufflation, also called pertubal insufflation, is generally regarded as of great diagnostic value in the investigation of sterility, especially if kymographic recording is available. The risk involved is considered very small, less than that of hysterosalpingography, while the therapeutic value is disputable. The indication for pertubal insufflation is sterility, where information as to tubal patency is desired, and early aftertreatment in tuboplasty. In cases of nonpatency, repeated insufflation may occasionally improve the passage by rupture of adhesions and dilatation of stenosed sections. The contraindications are the same as for hysterosalpingography: acute or subacute pelvic inflammation, menstrual or other genital bleeding, severe colpitis or cervicitis, general disease, and a raised sedimentation rate in cases of suspected active genital disease. Previous adnexal infection is no contraindication, provided that the disease has been quiescent for six to twelve months.

The author gives the results of 342 pertubal insufflations performed on 291 patients. The incidence of complications (3 per cent) was surprisingly high. Death in consequence of the test did not occur, but 11 cases of unquestionable pelvic inflammations were ascertained in 342 insufflations. Only 2 patients required admission to the hospital; the remaining 9 were treated as outpatients. A normal kymographic curve gives considerable certainty of patent tubes, according to the author; yet, in his experience, about 5 per cent of normal patency are revealed by hysterosalpingography as nonpatent. When nonpatency is ascertained by pertubal insufflation, therefore, the examination should be repeated or hysterosalpingography performed. In the present series the therapeutic value of pertubal insufflation proved to be small, conception having been obtained in no more than 1 per cent of cases.

ROBERT E. L. NESBITT, JR.

Zettergren: The Histogenesis of Uterine Myomas, p. 366.

During the last half of the Nineteenth Century there was a great deal of discussion about the histogenesis of uterine myomas, but the discussion died down at the beginning of the Twentieth Century, mostly because of the results published by Robert Meyer in 1907. He admitted that although uterine myomas might occasionally spring from the muscles of the vascular walls, the great majority of these tumors, in his opinion, originate from immature muscle cells, not encapsulated in the interfascicular connective tissue, but enclosed in the muscle bundles, especially in the small bundles close beside the large uterine veins. During recent years the discussion on this matter has flared up again. After a short review of different opinions concerning the histogenesis of uterine myomas, the author describes a case which is well suited for throwing some light on their origin. The tumors were not only numerous, most of them were extremely small. Likewise, the bundles of uterine muscle were separated from the vessels in the cords which bridged the space between the necrotic myoma and the unaltered myometrium. Serial sectioning disclosed that the tumor continued into a bundle of ordinary muscle cells which encircled the vessel. The author believes that the evidence (well documented by photomicrographs) presented by this case supports Meyer's theory that myomas do not spring from the vascular walls of the intrauterine vessels but from the uterine muscle cells situated in the immediate neighborhood of the vessels. There was no histologic evidence to support the contention that uterine myomas are derived from "immature" muscle cells. The author concludes

that it is hardly probable that the histogenesis of these tumors varies with their situation and, for this reason, the observations in the present case are applicable to uterine myomas situated in the ordinary way.

ROBERT E. L. NESBITT, JR.

Zachariae: Vaginitis Emphysematosa, p. 393.

Vaginitis emphysematosa is characterized by numerous gas-filled cysts in the vaginal connective tissue, many of which are situated just beneath the epithelium, thus projecting as densely packed, bluish gray cysts. The diameter varies from microscopic measurements to almost 2 cm. As a rule the lesion is limited to the portio vaginalis and the upper half or two-thirds of the vagina. In several cases, however, the entire vaginal wall has been involved. In many sites, the tense cysts are so densely packed that the vaginal wall feels stiff and infiltrated. There is no tenderness or crepitation to palpation. Histologically, there may be a severe leukocytic infiltration around the gas-filled cysts, almost exclusively eosinophilic in type. The cysts show no epithelial or endothelial border, but the connective tissue is pressed aside, forming a well-marked layer of flattened connective-tissue cells. Giant cells may be present, especially in an area where the cells have almost disappeared. This is an extremely characteristic lesion, the etiology of which still remains obscure, although the disease has been known for more than 100 years. On the basis of the literature and 2 cases of his own, the author discusses the occurrence, clinical features, pathology, and anatomy of the disease.

ROBERT E. L. NESBITT, JR.

Trolle: Clinical Usefulness of Vulvar Fluorescence for Estimation of Estrogenic Activity, p. 404.

It is well known that in some monkeys the female has glaring colors of the sex skin, colors that change with rhythmic regularity during the menstrual cycle. These phenomena have been found to be dependent on the influence of sex hormones, being provoked by estrogens (and testosterone) and depressed by progesterone. The vulvar fluoresence which is observable in women possibly constitutes a kindred reaction to the color changes of the sexual skin in monkeys. The author has made an investigation of the vulvar fluorescence during the normal menstrual cycle, during the latter three months of pregnancy, in elderly postmenopausal women, and castrates before and after administration of different estrogens and progesterone, and in a postmenopausal woman with an estrogen-producing ovarian carcinoma. A marked qualitative difference was seen between the vulvar fluorescence in women of the fertile age and that in elderly postmenopausal women or castrates. Further, it was shown that the purple fluorescence characteristic of the fertile women can be brought about in postmenopausal women or castrates by administration of estrogens, but there is no definite correlation, according to the author, between the purple fluorescence and the excretion of estrogens in urine. Nor has there been any difference between the purple fluorescence in pregnant women and that in nonpregnant fertile women. Estrogen-producing ovarian tumors may elicit purple fluorescence after the menopause. By determining the fluorescence it is possible to obtain in a quick and simple way an idea of the estrogenic activity in the women concerned. Owing to the aforementioned disadvantages, however, the author believes that the method is hardly likely to become of practical interest.

ROBERT E. L. NESBITT, JR.

Borglin: On the Metabolism of Choline in Pregnancy, p. 424.

Choline is a vitamin which has aroused increasing interest during the last few decades. Choline deficiency is known to cause sterility, and it is thought that there may be some interaction between estrogenic substances and choline. During pregnancy the hormone balance undergoes profound changes, including an increased production and an

increased elimination of estrogenic substances. The author believed that an investigation of the choline metabolism in pregnant women might help to elucidate any relationship between choline and estrogenic substances. He conducted an investigation of the urinary excretion of choline in 86 pregnant women and of the free choline in the blood during the last few months of pregnancy in 11 women. The excretion of choline increased throughout pregnancy, after which it soon returned to normal. During the last few months of pregnancy, this increase, which was readily demonstrable after the fourth or fifth month, was as much as five to ten times the normal amount. The increase in the excretion of choline during pregnancy was not influenced by complicating toxemia or diabetes mellitus, and was the same for single as for twin pregnancies. Pregnancy was not accompanied by any change in the amount of free choline in the blood. The author concluded that the increase in the excretion of choline in the urine during pregnancy is probably ascribable to an increased choline metabolism due to an increased production of estrogenic hormones.

ROBERT E. L. NESBITT, JR.

Dyggve, Dam, and Søndergaard: Influence on the Prothrombin Time of Breast-Fed Newborn Babies of One Single Dose of Vitamin K, or Synkayvite, Given to the Mother Within Two Hours After Birth, p. 440.

It has long been known that the rise in prothrombin time which usually occurs in breast-fed newborn babies during the first days after birth can be avoided by suitable treatment of the mother with vitamin K before delivery. This is usually believed to be due to transfer of vitamin K through the placenta, although the small amounts of active vitamin K substances found in the milk after ingestion of vitamin K preparations are also believed to play an important part in the provision of the infant with vitamin K. The authors observed that when given to the mother soon after delivery, vitamin K_1 and Synkayvite have almost no influence on the prothrombin time of the breast-fed newborn infant in the first two days, whereas there is a slight improvement on the third day and a marked improvement on the fourth, fifth, and sixth days. When given ante partum, the improvement of the prothrombin times begins earlier and is more marked. When vitamin K is given to the mother after delivery, the influence on the prothrombin time of the newborn is nil or almost nil during the first two days. This finding is explained by the fact that the consumption of milk is negligible during that period. The experiments indicate, however, that some vitamin K must have passed into the milk of the mother. The author concluded that the observed action via the breast milk is not sufficient to explain the whole effect of ante partum treatment; therefore, it is likely that in this form of treatment small amounts of vitamin K pass through the placenta.

ROBERT E. L. NESBITT, JR.

Fredrikson and Anberg: Delivery of Elderly Primigravidas, p. 483.

Because there are more elderly primigravidas now than there used to be, partly because of more late marriages, the many problems connected with the delivery of these patients are of great interest to the obstetrician. The authors reviewed the records of 433 primigravidas 35 years of age or over admitted to their service during the years 1947 to 1953. The elderly primigravidas made up 2.8 per cent of the total number of patients delivered in the department and 6.3 per cent of all the primigravidas. An equal number of primigravidas between 18 and 25 years of age distributed similarly over these years and chosen at random was used as a control series. Comparison between a series of young primigravidas and primigravidas 35 years old or more revealed that there was no definite difference in the rate of toxemia of pregnancy. Breech presentations were more common among the elderly women, occurring in 6 per cent as opposed to 3 per cent of the young primigravidas. The length of labor in the elderly was 26 hours on the average

against 16 hours in the younger group. Complications necessitating forceps delivery occurred much more often in elderly primigravidas, in 18 per cent as opposed to 3 per cent in the younger women. There were indications for cesarean section in a larger number of cases, in 14 per cent of the older group as against 1.1 per cent in all the pregnancies managed in the department. In the majority of the former cases cesarean section was done on account of the mothers' advanced age combined with some other indication, such as primary uterine inertia, breech presentation, prolonged sterility, and rupture of the membranes while the fetal head was still mobile and above the inlet. In the group of elderly primigravidas, 12 infants, or 2.9 per cent, died during or after delivery, 8 of them from asphyxia, 2 from rupture of the tentorium. Six infants, or 1.5 per cent, were lost in the young primigravid group. The authors concluded that an elderly primigravida should be given careful consideration at the beginning of labor and watched carefully so that obstetric intervention may be done in good time and in the interests of the fetus. According to the authors, the fetal loss noticed among elderly primigravidas could have been reduced only by more cesarean sections.

ROBERT E. L. NESBITT, JR.

Kjessler: The Time Factor in Rupture of the Membranes and Its Influence on Perinatal Fetal Mortality, p. 495.

One of the most important problems in obstetrics, the selection of the optimal time for rupture of the membranes and the influence thereof on perinatal fetal mortality, was investigated by this author. The study is based on 361 perinatal deaths among 12,325 singletons delivered during the years 1947 to 1949 in Gothenburg. The importance of the length of the interval between rupture of the membranes and birth of the infant in relation to the prognosis for mother and infant is discussed in detail. With the exception of cases where premature rupture of the membranes accounts for premature labor resulting in the birth of a feeble infant or where it is an etiological factor in prolapse of the cord, the condition appears to play a minor part as an underlying cause of perinatal fetal death. Yet it assumes major importance when other underlying causes of perinatal fetal death are also present, particularly prolonged labor and an unduly long interval from escape of the waters to the birth of the infant. The over-all incidence of premature rupture of the membranes in cases of single pregnancy was 18.9 ± 1.9 per cent during the period covered by this series. It was found that serious complications of labor tend to occur where the interval between rupture of the membranes and birth of the child is unduly long and, for this reason, these cases form a special group for consideration in this investigation. The term "long interval" (LI) denoted an interval between membrane rupture and birth of the infant exceeding 17 hours. The over-all incidence of LI in cases of single pregnancy was 10.1 ± 1.4 per cent. The most common conditions acting jointly with LI to cause perinatal fetal death were protracted labor and uterine inertia. The combination of LI, protracted labor, and uterine inertia was encountered in 80.4 per cent of the cases. Analysis of the 51 cases in the perinatal death series where LI was viewed as one of the underlying causes of perinatal fetal death, showed that the duration of labor was abnormally long in 44 and that uterine inertia was present in 41 cases. Inflammation of the respiratory tract formed the largest group of "terminal causes." Next in frequency were intracranial lesions which, with few exceptions, were associated with rupture of the tentorium. Intrauterine infection, clinically or histologically verified, was present in more than half of the cases. In order to obviate infection of the uterine cavity in connection with escape of the waters, chemotherapy and/or antibiotics were recommended by the author. All evidence indicates that treatment should be commenced before intrauterine infection produces symptoms. As labor is generally very difficult and complicated in these cases, vigilant obstetric care is a sine qua non, particularly in cases of elderly primiparas. Antenatal care should include timely radiography to investigate whether there is contracted pelvis and whether the size of the fetus involves danger of cephalopelvic dis-

proportion in cases of protracted gestation. In case of malpresentation, delivery by cesarean section should be considered, especially when the patient is an elderly primigravida.

ROBERT E. L. NESBITT, JR.

Jedberg: Female Genital Tuberculosis and Pregnancy, p. 535.

Sterility is the most common and important sequela of female genital tuberculosis. Today there is reason to hope that vigorous, modern, and early treatment with chemotherapeutics and antituberculosis agents will decrease the frequency of infertility in female genital tuberculosis. A closer search for genital tuberculosis by routine examination of all women with other genital tuberculous manifestations would probably reveal a fair number of silent cases in which early chemotherapy would probably produce recovery with preservation of fertility. In a sanatorium series, the author found silent genital tuberculosis in 3 per cent of women. The author surveys cases published in the literature of genital tuberculosis and extrauterine pregnancy, genital tuberculosis and pregnancy that ended in abortion, and the pregnancy that went on to term. It was stressed that reports are now beginning to appear of pregnancies in women with genital tuberculosis treated with modern antituberculosis agents. The author contributed a personal case in which pregnancy occurred twice, once with delivery at term, following left salpingo-oophorectomy and right tubal resection for tuberculous salpingitis. He believed that the risks of complications from tuberculosis during pregnancy, delivery, and the puerperium are no longer great and that medication also appears to offer protection to the infant. In the author's opinion, surgery should be as conservative as possible in women of fertile age. Most of the earlier comparisons of genital tuberculosis series are based on old cases diagnosed late and healed with defects. They therefore give far too gloomy a picture of the situation. With modern diagnostic methods and therapeutic possibilities there is reason to hope that the situation will be even brighter in the future.

ROBERT E. L. NESBITT, JR.

Brosset: Maternal Morbidity and Fetal Mortality Associated With Breech Delivery, p. 546.

It has long been agreed that the risk to the fetus is greater when delivered as a breech than as a vertex. The author compares carefully selected material from vertex deliveries, the occiput anterior, with identically selected material from breech deliveries. The investigation is based on 24,746 cases of single pregnancy delivered spontaneously during the years 1935 to 1944. Maternal morbidity and fetal mortality in breech delivery were investigated on the basis of 559 breech deliveries among a total of 19,154 cases selected from the previously mentioned total deliveries. In the remaining cases the fetus was delivered as a vertex with the occiput anterior. A comparative study of the findings in the two groups showed that the risk to the mother was not greater in breech delivery while the danger to the fetus was considerably increased. The incidence of threatened intrauterine asphyxia was much higher in elderly multiparas when delivery was by the breech than by the vertex with the occiput anterior. The incidence of intrapartum and postpartum hemorrhage appeared to be slightly lower in all groups of breech delivery. The risk to the fetus when delivered as a breech in primiparas appeared to be four times and in multiparas ten times that of delivery as a vertex with the occiput anterior. Fetal mortality in breech delivery was found to be higher in multiparas (7.3 per cent) than in primiparas (5.9 per cent) in the present series. Because the birth weight of one half of the stillborn infants of elderly primiparas was more than 4,000 grams, the author assumes that this factor was concerned in the remarkably high fetal mortality rate in this group. Of all groups investigated, the lowest fetal mortality rate (2.0 per cent) was recorded in young multiparas.

ROBERT E. L. NESBITT, JR.

Dahlberg: Adenocarcinoma in One Horn of Uterus Duplex, p. 563.

The first mention of a case of cancer in the right horn of a uterus didelphys was by Hofmeier (1902) who diagnosed the condition at autopsy. The first case diagnosed by hysterography was reported in 1950 by Siegler who, while investigating a 29-year-old woman for sterility, found an adenocarcinoma in the left horn of a uterus didelphys. The author reports 3 cases of cancer in one horn of a uterus duplex, where the correct diagnosis was successfully made by hysterography, and one borderline case. It seems vital to the author to perform a hysterogram in cases of endometrial carcinoma. Not only can the growth be mapped, but in cases similar to the ones described adequate treatment can be given by packing the radium in the correct location. Subsequent hysterograms show to what extent treatment has been successful.

ROBERT E. L. NESBITT, JR.

Estudios sobre Esterilidad

Vol. 7, May-December, 1956.

*Bravo, A. A.: Retroversion of the Uterus as a Cause of Sterility, p. 65.

Bravo: Retroversion of the Uterus as a Cause of Sterility, p. 65.

The author studied 7,062 consecutive women and found the incidence of retroversion of the uterus to be 18.7 per cent. The incidence of retroversion of the uterus in 1,850 married women who were sterile was 18 per cent and the incidence of retroversion in 5,212 women who had had 1 to 14 pregnancies was 18.9 per cent. Thus he concluded that there was no significant difference between the groups. Among 697 women who had presented themselves because of sterility, 42 cases were found to be due to male causes, and among the remaining 655 women, the incidence of retroversion was 17.7 per cent. After thoroughly studying this last group, he found that in only 1.8 per cent was retroversion the only abnormality present, but that in the other 98.2 per cent there were other abnormalities in addition to the retroversion. The conclusion drawn is that retroversion of the uterus can only occasionally be the cause of sterility.

FRANCIS B. O'BRIEN

Zentralblatt für Gynäkologie

Volume 78, October 27, 1956.

Kloos, K., and Wulf, H.: Hyaline Membrane Disease in the Newborn, p. 1693.

Hoffbauer, H.: The Importance of Examination of Amniotic Fluid for the Diagnosis and Treatment of Erythroblastosis Fetalis, p. 1707.

Merdler-Paltin, K.: The Physiology and Management of Hyperoxemic, Nonasphyctic Apnea of the Newborn, p. 1713.

*Klees, E., and Heinke, E.: The Development of Children Whose Fathers Received High Doses of Testosterone to Aid Fertility, p. 1726.

Schulze, E. E.: Early Induction of Labor in Cephalopelvic Disproportion, p. 1731.

Klees, and Heinke: The Development of Children Whose Fathers Received High Doses of Testosterone to Aid Fertility, p. 1726.

The question has been raised as to whether or not hormone treatment of parents can cause disturbances in the development of their offspring. The authors report on 6 children conceived after their fathers had been treated with testosterone because of oligospermia. No detrimental effect on any of the children has been recorded.

WALTER F. TAUBER

ITEMS

Seventh International Cancer Congress

The Seventh International Cancer Congress, sponsored by the International Union Against Cancer, will be held in London, England, July 6-12, 1958, under the Presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress:

A. Experimental
B. Clinical and Cancer Control

Special emphasis will be placed on Hormones and Cancer, Chemotherapy, Carcinogenesis, and Cancer of the Lung.

Proffered papers will be considered only if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if dealing with new and unpublished work.

The registration fee for the Congress will be 10 pounds or $30 and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to

THE SECRETARY GENERAL
SEVENTH INTERNATIONAL CANCER CONGRESS
45 LINCOLN'S INN FIELDS
LONDON, W. C. 2, ENGLAND

American Board of Obstetrics and Gynecology

Applications for certification, new and reopened, for the 1958 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is Sept. 1, 1957. No applications can be accepted after that date.

Candidates for admission to the Examinations are required to submit with their application a typewritten list of all patients admitted to the hospitals where they practice for the year preceding their application or the year prior to their request for reopening of their application. This information is to be attested to by the Record Librarian of the hospital or hospitals where the patients are admitted and submitted on paper 8½ by 11 inches. Necessary detail to be contained in the list of admissions is outlined in the Bulletin and must be followed closely.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

ROBERT L. FAULKNER, M.D., SECRETARY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January and July)

American College of Obstetricians and Gynecologists. (1951) *President,* R. Gordon Douglas, New York, N. Y. *Secretary,* John C. Ullery, 15 S. Clark St., Chicago 3, Ill. Next clinical meeting, Hotel Statler, Los Angeles, Calif., April 21-23, 1958.

American Gynecological Society. (1876) *President,* Norman F. Miller. *Secretary,* Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C. Annual meeting, Grove Park Inn, Asheville, N. C., May 19-21, 1958.

American Association of Obstetricians and Gynecologists. (1888) *President,* F. Bayard Carter, Durham, N. C. *Secretary,* E. Stewart Taylor, 4200 E. Ninth Ave., Denver 20, Colo. Annual meeting, The Homestead, Hot Springs, Va., Sept. 5-7, 1957.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Arthur B. Hunt, Rochester, Minn. *Secretary,* Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Annual meeting, Hotel Fontenelle, Omaha, Neb., Oct. 24-26, 1957.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* Manly E. Hutchison, Columbia, S. C. *Secretary,* W. Norman Thornton, Jr., Dept. of Obstetrics and Gynecology, University of Virginia, Charlottesville, Va. Next meeting, Hollywood Beach Hotel, Hollywood, Fla., Feb. 1-5, 1958.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* D. F. Kaltreider. *Secretary,* Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Meetings with annual A.M.A. meetings.

Society of Obstetricians and Gynaecologists of Canada. (1944) *President,* Brian D. Best, Winnipeg, Manitoba. *Secretary,* F. P. McInnis, 280 Bloor St. W., Toronto, Ont. Annual meeting, The Algonquin, St. Andrews-by-the-Sea, New Brunswick, June 19-22, 1958.

American Board of Obstetrics and Gynecology, Inc. (1930) *President,* Bayard Carter. *Secretary,* Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6, Ohio.

Akron Obstetrical and Gynecological Society. (1946) *President,* E. A. Riemenschneider. *Secretary,* Louis M. Walker, 1108 Second National Bldg., Akron 8, Ohio. Meetings, January, April, July, and October.

Alabama Association of Obstetricians and Gynecologists. (1940) *President,* Buford Word, Birmingham, Ala. *Secretary,* Julian P. Hardy, 920 S. 19th St., Birmingham 5, Ala.

Alameda County Gynecological Society. (1951) *President,* Wilson Footer. *Secretary,* Emery P. Page, 3031 Telegraph Ave., Berkeley 5, Calif. Meetings, fourth Wednesday of each month.

Arkansas Obstetrical and Gynecological Society. (1953) *President,* Haynes Jackson. *Secretary,* Robert McCrary, Hot Springs, Ark. Meetings, April and October.

Atlanta Obstetrical and Gynecological Society. (1954) *President,* John B. Cross. *Secretary,* William H. Grimes, Jr., 272 Boulevard, N. E., Atlanta 12, Ga. Meetings, January, April, June, and October.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* Ernest B. Oliver. *Secretary,* Eugene Howe, 920 S. 19th St., Birmingham 5, Ala. Meetings four times a year.

Boston, Obstetrical Society of. (1861) *President,* Paul A. Younge. *Secretary,* A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, January, February, March, April, October, and November.

Bronx Gynecological and Obstetrical Society. (1924) *President,* John S. Giaccone. *Secretary,* Sidney S. Steckel, 930 Grand Concourse, New York, N. Y. Meetings, fourth Monday, Concourse Plaza Hotel.

Brooklyn Gynecological Society. (1890) *President,* Henry Mehldau. *Secretary,* Warren A. Lapp, 731 E. 22nd St., Brooklyn 10, N. Y. Meetings, third Wednesday, October, November, January, February, March, April, and May.

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*Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* Robert E. O'Connor. *Secretary,* Chester Kaminski, 333 Linwood Ave., Buffalo 9, N. Y. Meetings, first Tuesday, October through May.

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Albert Van Ness. *Secretary,* James Covell, 753 James St., Syracuse, N. Y. Meetings, second Tuesday, January, March, May, September, and November.

Chicago Gynecological Society. (1878) *President,* A. F. Lash. *Secretary,* Clyde J. Geiger, 4753 Broadway, Chicago 40, Ill. Meetings, third Friday, October through June.

Cincinnati Obstetrical and Gynecological Society. (1876) *President,* Robert R. Pierce. *Secretary,* Edward Alberts, 199 Wm. Howard Taft Rd., Cincinnati 19, Ohio. Meetings, third Thursday, September through June.

Cleveland Society of Obstetrics and Gynecology. (1947) *President,* Ralph Dial. *Secretary,* Richard Glove, 20119 Van Aken Blvd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.

Columbus Obstetric-Gynecologic Society. (1944) *President,* James B. Patterson. *Secretary,* Harry E. Ezell, Jr., 81 S. Fifth St., Columbus, Ohio. Meetings, last Wednesday of month, September through May, except December.

Connecticut Society of American Board Obstetricians and Gynecologists, Inc. (1952) *President,* Lewis P. James. *Secretary,* Joseph Klein, 435 Farmington Ave., Hartford 5, Conn. Meetings, April and November.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* W. K. Strother. *Secretary,* H. I. Kantor, 3534 Maple Ave., Dallas 19, Texas. Meetings, spring and fall.

Dayton Obstetrical and Gynecological Society. (1937) *President,* H. E. McKnight. *Secretary,* James Burt, 201 S. Main St., Dayton 2, Ohio. Meetings, third Wednesday each month.

Denver Gynecological and Obstetrical Society. (1942) *President,* W. F. Manly. *Secretary,* Alvin J. Frosh, 2222 East 18th Ave., Denver, Colo. Meetings, first Monday of every month, October through May, inclusive.

El Paso County Obstetrical and Gynecological Society. (1948) *President,* Erich Spier. *Secretary,* Alvin L. Perry, 209 Medical Arts Bldg., El Paso, Texas. Meetings bimonthly.

Florida Obstetric and Gynecologic Society. (1948) *President,* S. Carnes Harvard. *Secretary,* T. Bert Fletcher, Jr., 1203 Miccosukee Rd., Tallahassee, Fla. Meetings, spring and winter.

Georgia State Obstetrical and Gynecological Society. (1951) *President,* Hartwell Boyd. *Secretary,* J. Lon King, Jr., 817 Persons Bldg., Macon, Ga. Meetings, spring and fall.

Harris, John Warton, Obstetrical Society. (1953) *President,* William R. Knight, III. *Joint Secretaries,* Madeline Thornton and William Keikhofer, State of Wisconsin General Hospital, 1300 University Ave., Madison, Wis. Annual meeting in May.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Rodney T. West. *Secretary,* Fugate Carty, Straub Clinic, Thomas Square, Honolulu, Hawaii. Meetings, third Monday of each month.

Houston Gynecological and Obstetrical Society. *President,* Donald M. Paton. *Secretary,* Melville L. Cody, 4115 Fannin St., Houston, Texas. Scientific meetings, January, March, and May. Business meeting, October.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* Sprague H. Gardiner. *Secretary,* John E. Mackey, 3209 N. Meridian St., Indianapolis 8, Ind. Meetings, January and October.

Interurban Obstetrical and Gynecological Society. (1949) *President,* Douglas Cannell. *Secretary,* E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, October, 1957.

Iowa Obstetrical and Gynecological Society. *President,* William C. Keettel, Iowa City, Iowa. *Secretary,* W. B. Goddard, University Hospitals, Iowa City, Iowa. Meetings, April and November.

Kansas City Gynecological Society. (1922) *President,* William C. Mixson. *Secretary,* Kenneth E. Nicolay, 4635 Wyandotte, Kansas City 12, Mo. Meetings, September, November, January, March, and May.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* Joseph Liebman, Frankfort, Ky. *Secretary,* Ed. Masters, 107 Fairmeade Rd., Louisville, Ky. Annual meeting in April.

Long Beach Obstetrical and Gynecological Society. (1954) *President,* Sydney G. Willner. *Secretary,* Lyle Gray, 8th and Pine Ave., Suite 419, Long Beach 13, Calif. Meetings, first Tuesday of March, June, September, and December.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Walter C. Rogers. *Secretary,* Dan Golenternes, 360 N. Bedford Dr., Beverly Hills, Calif. Meetings, second Tuesday, September, November, January, and March.

Louisville Obstetrical and Gynecological Society. *President,* Hugh P. Adkins. *Secretary,* Douglas M. Haynes, 323 E. Chestnut St., Louisville 2, Ky. Meetings, fourth Monday, September, October, November, January, February, March, April, and May.

Madison Obstetrical and Gynecological Society. (1950) *President* and *Secretary,* William C. Mussey, 113 N. Carroll St., Madison, Wis. Meetings, first Tuesday each month, September through June.

Maryland, Obstetrical and Gynecological Society of. (1929) *President,* Royce Hodges. *Secretary,* Harry M. Beck, 700 N. Charles St., Baltimore 1, Md. Meetings, October, December, February, and May.

Memphis Obstetrical and Gynecological Society. (1950) *President,* Carey Bringle. *Secretary,* Robert M. Ruch, 899 Madison Ave., Memphis, Tenn. Meetings, second Tuesday, September, October, November, January, February, March, and May.

Miami Obstetrical and Gynecological Society. (1946) *President,* William Howdon. *Secretary,* John Schultz, Huntington Bldg., Miami, Fla. Meetings, second Thursday, January, March, May, and November.

Michigan Society of Obstetricians and Gynecologists. (1924) *President,* Lester E. Bauer. *Secretary,* E. Bruce Foster, 853 Fisher Bldg., Detroit 2, Mich. Meetings, first Tuesday, October through May.

Milwaukee Gynecological Society. (1951) *President,* Roland S. Cron. *Secretary,* Carlton W. Wirthwein, 425 East Wisconsin Ave., Milwaukee 2, Wis. Meetings, last Monday, January, March, May, and November.

Minneapolis Obstetrical and Gynecological Society. (1955) *President,* John A. Haugen. *Secretary,* Francis M. Swain.

Minnesota Obstetrical and Gynecological Society. *President,* Frederick L. Schade. *Secretary,* Edward A. Banner, 200 First Ave., S.W., Rochester, Minn. Next meeting, Town and Country Club, St. Paul, Minn., Nov. 30, 1957.

Mississippi Obstetrical and Gynecological Society. (1947) *President,* Ross F. Bass, Jackson, Miss. *Secretary,* Blanche Lockard, 625 Fondren Pl., P. O. Box 4325, Jackson, Miss. Meetings, spring and fall.

Mobile County Obstetrical and Gynecological Society. (1949) *President,* O. M. Otts, Jr. *Secretary,* A. K. Conditt, 1367 Government St., Mobile, Ala. Meetings, quarterly when called.

Montgomery County (Ohio) Obstetrical and Gynecological Society. (1937) *President,* L. O. Fredericks. *Secretary,* A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.

Montana Obstetrical and Gynecological Society. (1946) *President,* Arnold E. Ritt, Missoula, Mont. *Secretary,* Robert H. Leeds, Chinook, Mont. Next meeting, Bozeman, Mont., May, 1958.

Nashville Obstetrical and Gynecological Society. (1955) *President,* Joe Anderson. *Secretary,* H. M. Pace, Jr., 610 Gallatin Rd., Nashville, Tenn. Meetings, February, June, October, and December.

Nassau Obstetrical Society. (1944) *President,* David G. Warden. *Secretary,* A. F. Rowsom, 21 Weir Lane, Locust Valley, N. Y. Meetings, second Monday, October, December, February, and April.

New England Obstetrical and Gynecological Society. (1929) *President,* Roland McSweeney. *Secretary,* William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Meetings, spring and fall.

New Haven Obstetrical and Gynecological Society. (1946) *President,* William Richards. *Secretary,* Virginia M. Stuermer, 42 Trumbull St., New Haven 10, Conn. Meetings, third Tuesday, September, November, January, March, and May.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Felix H. Vann. *Secretary,* Paul Grossbard, 162 Lexington Ave., Passaic, N. J. Meetings, October and April.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* James W. Wiggins. *Secretary,* Robert P. George, 4800 Gibson Blvd., S. E., Albuquerque, N. Mex. Meetings, quarterly.

New Orleans Gynecological and Obstetrical Society. (1924) *President,* Abe Mickal. *Secretary,* Julius T. Davis, Jr., 4414 Magnolia St., New Orleans, La. Meetings, October, November, January, March, and May.

New York Obstetrical Society. (1863) *President,* Edward H Dennen. *Secretary,* George L. Bowen, 101 East 74th St., New York 21, N. Y. Meetings, second Tuesday, October through May.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* H. Fleming Fuller. *Secretary,* James A. Crowell, 412 N. Church St., Charlotte 2, N. C. Meeting, Mid Pines Club, Southern Pines, N. C., April 25-27, 1958.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* C. B. Darner. *Secretary,* John Gillam, Box 1388, Fargo, N. D. Next meeting, Sept. 13-14, 1957.

Northeastern New York Obstetrical and Gynecological Society. (1935) *President,* Paul Schultze, Jr. *Secretary,* Thomas F. D'Aurio, 17 State St., Troy, N. Y. Meetings, third Thursday, January, May, and October.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* Robert D. Anspaugh. *Secretary,* Sterling T. Crawford, 1200 N. Walker, Oklahoma City, Okla. Meetings, third Wednesday of February, April, October, and December.

Omaha Obstetrical and Gynecological Society. (1947) *President,* W. Riley Kovar. *Secretary,* W. H. Taylor, Jr., 3807 Cuming St., Omaha 31, Neb. Meetings, third Wednesday, January, March, May, October, and November.

Oregon Society of Obstetricians and Gynecologists. *President,* J. Oppie McCall, Jr. *Secretary,* Otto R. Emig, Rt. 1, Box 281, Lake Grove, Oregon. Meetings, third Friday, October through May, except December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Bernard J. Hanley, Los Angeles, Calif. *Secretary,* Donald W. DeCarle, 2000 Van Ness Ave., San Francisco, Calif. Next meeting, El Mirador Hotel, Palm Springs, Calif., Oct. 30-Nov. 2, 1957.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* J. E. Harrison. *Secretary,* Earl L. Hall, 1220 Central Ave., Great Falls, Mont.

Philadelphia, Obstetrical Society of. (1868) *President,* Robert M. Hunter. *Secretary,* John P. Emich, Jr., 155 W. Walnut Lane, Philadelphia 44, Pa.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* John C. Hughes. *Secretary,* Michael A. Guthrie, 128 Carlton House, 550 Grant St., Pittsburgh 19, Pa. Meetings, first Monday, October through May, except January.

Portland Society of Obstetricians and Gynecologists. (1928) *President,* Theodore W. Adams. *Secretary,* J. Oppie McCall, Jr., Standard Insurance Bldg., Portland, Ore. Meetings, fourth Wednesday, September through May.

Queens Gynecological Society. (1948) *President,* Joseph Gaetane. *Secretary,* David A. Connors, 166-05 Highland Ave., Jamaica 32, N. Y. Meetings, second Wednesday, October, December, February, and April.

Rochester Academy of Medicine, Obstetrics and Gynecology Section. (1939) *President,* Robert Corcoran. *Secretary,* John G. Hamilton, 265 Alexander St., Rochester 7, N. Y.

St. Louis Gynecological Society. (1924) *President,* John E. Hobbs. *Secretary,* George Wulff, 8505 Delmar Blvd., St. Louis 24. Meetings, second Thursday, October, December, February, and April.

San Antonio Obstetrical and Gynecological Society. *President,* G. G. Passmore. *Secretary,* Frank M. Posey, Jr., 641 Moore Bldg., San Antonio, Texas. Meetings, first Monday of the month.

San Diego Gynecological Society. (1937) *President,* Wayne B. Henderson. *Secretary,* Albert P. Kimball, 505 Maple St., San Diego, Calif. Meetings, as announced.

San Francisco Gynecological Society. (1929) *President,* Robert D. Dunn. *Secretary,* Carl Goetsch, 2340 Ward St., Berkeley, Calif. Meetings, second Friday, October through April.

Seattle Gynecological Society. (1941) *President,* John Clancy. *Secretary,* Paul G. Peterson, 1664 Medical-Dental Bldg., Seattle 1, Wash. Meetings, third Wednesday, January, March, April, May, September, October, and November.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* Herbert Blake. *Secretary,* James E. Bell, Jr., 325 W. Calhoun St., Sumter, S. C. Meeting, Nov. 2-3, 1957.

Southern California, Obstetrical and Gynecological Assembly of. (1945) *President,* Daniel G. Morton, Los Angeles, Calif. *Secretary,* Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, Los Angeles, Feb. 10-14, 1958.

Southwest Obstetrical and Gynecological Society. (1951) *President,* Jesse Rust, San Diego, Calif. *Secretary,* Zeph B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Next meeting, Las Vegas, Nev., November, 1957.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Arthur M. Faris. *Secretary,* Oran V. Prejean, 1317 N. Washington Ave., Dallas 4, Texas. Annual meeting, Galveston, Texas, February, 1958.

Tulsa Obstetrical and Gynecological Society. (1955) *Vice President,* Hall Ketchum. *Secretary,* J. E. Goldberg, 212 Utica Square Medical Center, Tulsa, Okla. Five meetings per year.

Utah Obstetrical and Gynecological Society. (1948) *President,* Fred D. Kartchner. *Secretary,* A. Krehl Smith, 975 East 2nd South, Salt Lake City, Utah. Meetings, second Thursday of October, December, February, and May.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Millard B. Savage. *Secretary,* Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk, Va. Meetings, April and October.

Washington Gynecological Society. (1933) *President,* Stafford W. Hawken. *Secretary,* Robert B. Nelson, Jr., 1824 Massachusetts Ave., N. W., Washington 6, D. C. Meetings, October, November, January, March, and May.

Washington State Obstetrical Association. (1936) *President,* Morton W. Tompkins. *Secretary,* Charles W. Day, 1420 Seneca, Seattle 1, Wash. Meetings, spring and fall.

West Texas Obstetrical and Gynecological Society. (1954) *President,* Joe L. Cornelison, San Angelo, Texas. *Secretary,* Tom C. Burditt, 1440 N. Third St., Abilene, Texas, Meeting, Dec. 7, 1957.

Westchester Obstetrical and Gynecological Society. (1939) *President,* Payson B. Ayers, Cos Cob, Conn. *Secretary,* Edwin A. Haverty, 328 Mamaroneck Ave., White Plains, N. Y. Meetings, second Wednesday, October, November, January, February, March, and May.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Alice Watts. *Secretary,* William V. Luetke, 1023 Regent St., Madison 5, Wis. Meetings, spring and fall.

CHEMOTHERAPY PLUS FLORA CONTROL

Floraquin®

Destroys Vaginal Parasites
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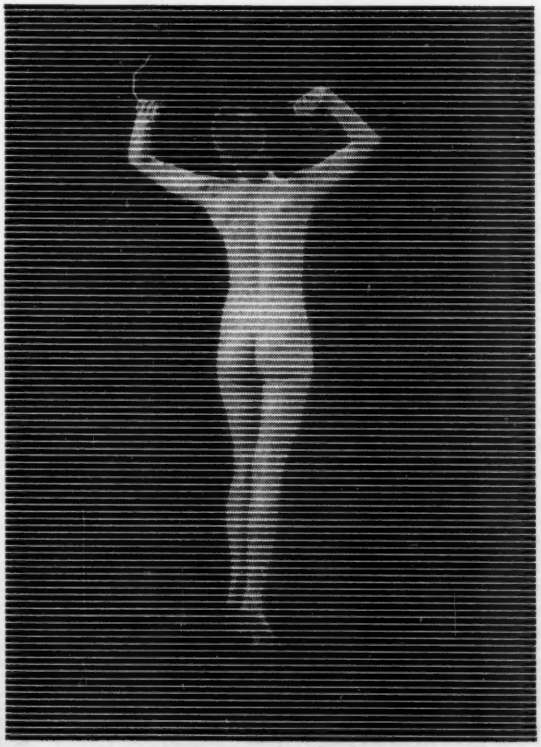

Vaginal discharge is one of the most common and most troublesome complaints met in practice. Trichomoniasis and monilial vaginitis, by far the most common causes of leukorrhea, are often the most difficult to control. Unless the normal acid secretions are restored and the protective Döderlein bacilli return, the infection usually persists.

Through the direct chemotherapeutic action of its Diodoquin® (diiodohydroxyquin, U.S.P.) content, Floraquin effectively eliminates both trichomonal and monilial infections. Floraquin also contains boric acid and dextrose to restore the physiologic acid pH and provide nutriment which favors regrowth of the normal flora.

Method of Use

The following therapeutic procedure is suggested: One or two tablets are inserted by the patient each night and each morning; treatment is continued for four to eight weeks.

Intravaginal Applicator for Improved Treatment of Vaginitis

This smooth, unbreakable, plastic device is designed for simplified vaginal insertion of Floraquin tablets by the patient. It places tablets in the fornices and thus assures coating of the entire vaginal mucosa as the tablets disintegrate.

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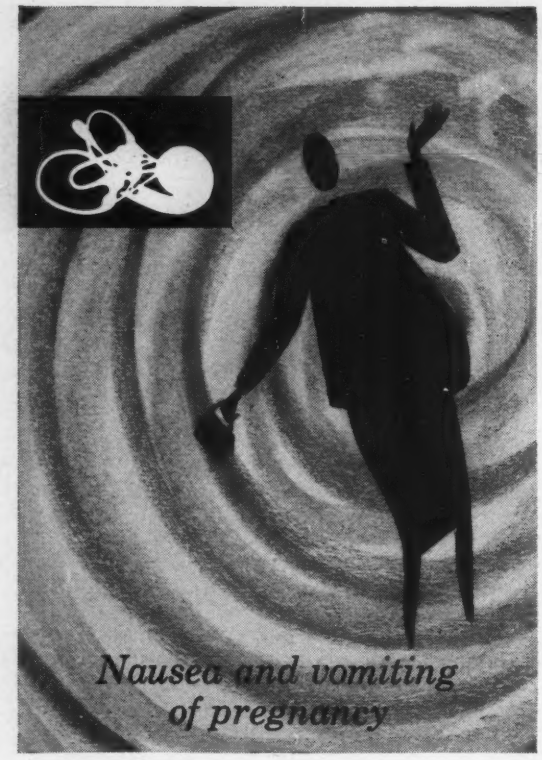

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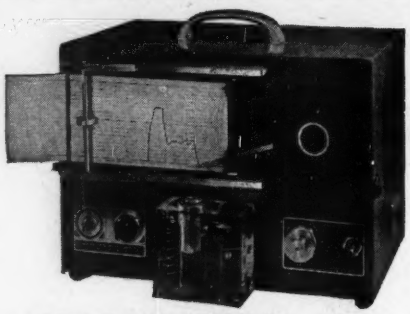

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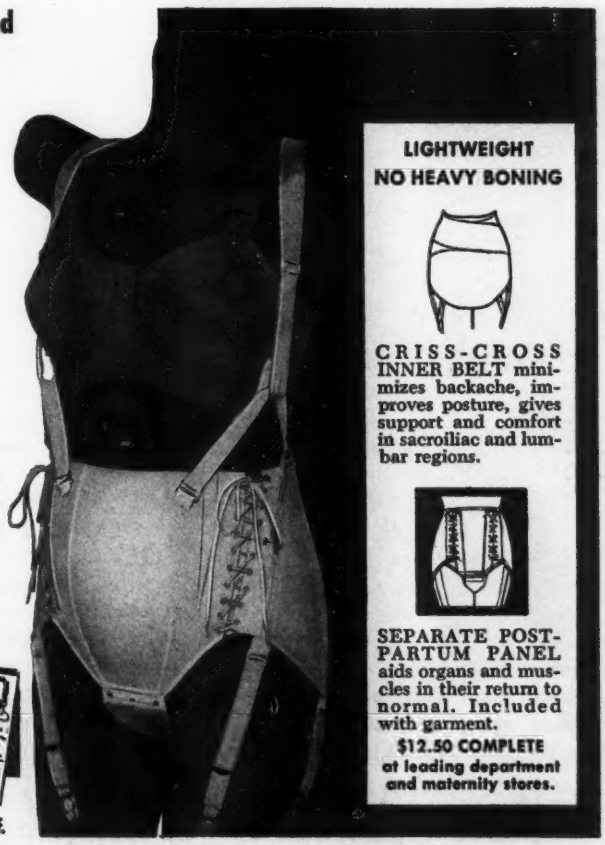

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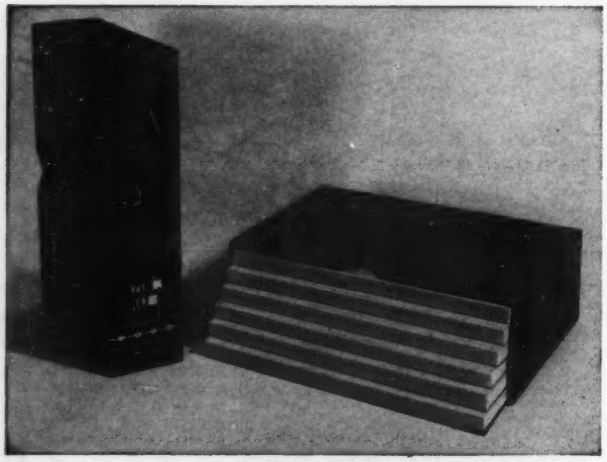

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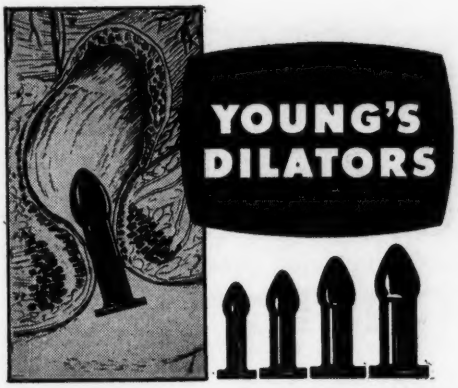

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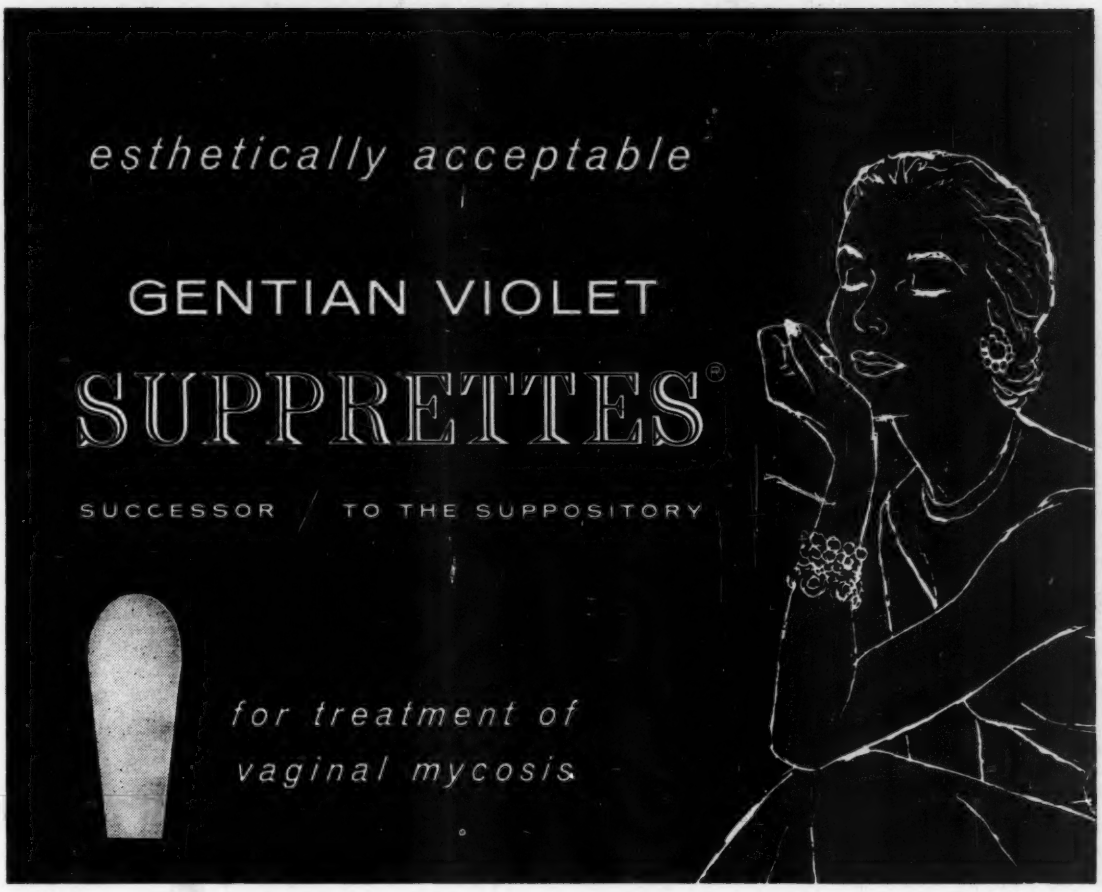

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